Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Developed by the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

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

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What's New in the Pediatric Guidelines (Last updated March 1, 2016; last reviewed March 1, 2016)

Key changes made by the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) to update the March 5, 2015, Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection are summarized below. Text and references have been updated throughout the document to include new data and publications where relevant. Minor changes and edits have been made to enhance clarity and facilitate use of the Guidelines. All new changes are highlighted.

Identification of Perinatal HIV Infection

- The Panel has provided additional explanation and has emphasized the new recommendations to use the fourth generation HIV testing platform as the initial test of choice for pregnant HIV-negative women.

Diagnosis of HIV Infection

- The Panel has clarified that recommended virologic testing at 1–2 months of age is preferably scheduled 2-4 weeks after cessation of antiretroviral (ARV) prophylaxis. In such situations, the test would be obtained at 6 weeks (in the case of 4 weeks of neonatal ARV prophylaxis) or at 2 months (in the case of 6 weeks of ARV prophylaxis).
- The Panel has updated information about Food and Drug Administration (FDA)-approved HIV diagnostic tests.

Clinical and Laboratory Monitoring of Pediatric HIV Infection

- Content has been reorganized according to the Panel's bulleted recommendations, followed by information about general considerations in immunologic and HIV RNA monitoring.
- The Panel's bulleted recommendations about antiretroviral drug resistance testing, as part of laboratory monitoring, have been moved into this section.
- Changes have also been made in accordance with the Panel's revised recommendations about when to initiate therapy in antiretroviral naive children.

When to Initiate Therapy in Antiretroviral-Naive Children

- Based on data from the multinational START and PENPACT1 trials, the Panel now recommends antiretroviral treatment (ART) for all HIV-infected children, regardless of clinical symptoms, viral load or CD4 T lymphocyte (CD4) count. The strength of the Panel's recommendations varies by age and pretreatment CD4 cell count due to fewer available pediatric data regarding benefits and risks of therapy in asymptomatic HIV-infected children than in adults.
- The text offers guidance on the urgency of initiation of ART based on age, clinical status and CD4 cell counts.

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

- Content has been reorganized to enhance usability, and a figure has been added to provide an overview of Preferred and Alternative regimens for initiation of ART in treatment -naive children.
- The Panel has added the tenofovir alafenamide (TAF) containing fixed dose combination tablet elvitegravir/cobicistat/emtricitabine/TAF (Genvoya) as a preferred integrase strand transfer inhibitor (INSTI) regimen in adolescents 12 years and older.

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- Darunavir boosted with ritonavir is now considered a preferred protease inhibitor (PI) in children and adolescents aged 3 years and older.
- Dolutegravir is now considered a preferred INSTI in adolescents aged 12 years and older.
- Raltegravir is now considered a preferred INSTI in children aged 2 to 12 years.
- The Panel has determined that fosamprenavir, nelfinavir, stavudine, and unboosted atazanavir should not be used for initial therapy; these drugs have been moved to the "What Not to Start" section.

Specific Issues in Antiretroviral Therapy for Neonates

- The Panel has updated this section with information about a recent study of nevirapine pharmacokinetics in premature infants and the dosing regimen for infants born between 34 and 37 weeks gestation to be studied in IMPAACT P1115.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents

- The Panel has reviewed and updated this section to harmonize with and complement content in the Adult and Adolescent Antiretroviral Guidelines.
- The Panel has changed to the use of sexual maturity rating (SMR), rather than Tanner staging, and has clarified that adolescents in early puberty (i.e., SMR I–III) should receive pediatric dosing, whereas those in late puberty (i.e., SMR IV–V) should follow adult dosing guidelines.
- Content has been added about timing and selection of ART, adherence concerns, and sexually transmitted infections in adolescents. Additional guidance has been provided about approaches to improve retention in care and minimize the risk of interruptions to ART during the transition from pediatric to adult HIV care settings.

Management of Medication Toxicity

- Toxicity table sections have been reviewed and updated throughout. Examples of notable changes include the following:
  - The Central Nervous System Toxicity Table has been updated to include dolutegravir-associated neuropsychiatric symptoms and new data on neuropsychiatric symptoms associated with rilpivirine in adolescents.
  - The Dyslipidemia Toxicity Table now includes information about TAF when given in combination with elvitegravir, cobicistat, and emtricitabine as a single tablet regimen (Genvoya) in adults and adolescents.
  - The Rash and Hypersensitivity Toxicity Table has been updated to include rash with hepatic dysfunction associated with dolutegravir and information about drug rash/reaction with eosinophilia and systemic symptoms (DRESS) associated with several different drugs.

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

- The Panel has condensed the section on the role of therapeutic drug monitoring by moving some information to relevant drug sections.

Antiretroviral Drug-Resistance Testing

- The Antiretroviral Drug-Resistance Testing section has been deleted. This content has been integrated in relevant sections throughout the guidelines with links to detailed information available in the Adult and Adolescent Antiretroviral Guidelines section on Drug-Resistance Testing.

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Pediatric Antiretroviral Drug Information

Drugs sections have been reviewed and updated to include new pediatric data and dosing information. Weight parameters or sexual maturity ratings for adolescent dosing have been added to drug tables where indicated. Information about Genvoya, a fixed dose combination of elvitegravir, cobicistat, emtricitabine, and TAF (approved by the FDA in November 2015), has been incorporated into each of those drug sections. A new drug section was added for TAF.

Nucleoside Analogue Reverse Transcriptase Inhibitors

- **Abacavir:** Children weighing at least 14 kg who can be treated with pill formulations can initiate therapy with once daily abacavir dosing. However, initiation of therapy with once daily abacavir liquid is not generally recommended. Refined guidance has been provided on the transition from twice daily to once daily dosing of abacavir after 6 months in clinically stable patients with undetectable viral load and stable CD4 cell counts. The section was also revised to follow FDA recommendations for use of adult doses of abacavir in children and adolescents weighing 25 kg or more.
- **Emtricitabine:** The section was updated to include information about the fixed dose combination, Genvoya, for use in persons aged ≥12 years and weighing at least 35 kg.
- **Lamivudine:** Based on a study demonstrating lower bioavailability of lamivudine oral solution versus tablets in pediatric patients, a statement was added to reinforce that once daily administration is not generally recommended in infants and young children being treated with lamivudine oral solution. The section was updated to follow FDA recommendations for use of adult doses of lamivudine in children weighing 25 kg or more.
- **TAF:** A new section was added for TAF based on FDA approval of the fixed dose combination Genvoya (emtricitabine, elvitegravir, cobicistat, and TAF) for use in persons aged ≥12 years and weighing at least 35 kg.
- **Tenofovir Disoproxil Fumarate (TDF):** The discussion about monitoring for potential renal toxicity has been updated. In clinical practice, renal tubular damage associated with TDF is perhaps easiest to identify using a renal dipstick to identify normoglycemic glycosuria and proteinuria.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

- **Nevirapine:** The Panel has added information about the investigational dose of nevirapine (not FDA approved) for premature infants born at 34–37 weeks gestation and less than one month of age.
- **Rilpivirine:** Dosing information has been updated to follow the FDA recommendation for use of adult doses of rilpivirine in adolescents 12 years and older weighing at least 35 kg.

Protease Inhibitors

- **Atazanavir:** The section has been updated based on FDA approval of atazanavir oral powder for use in children 3 months of age and older weighing at least 5 kg and in children weighing 25 kg or more who cannot swallow pills. Atazanavir oral powder must be given with ritonavir. Information about Evotaz, a fixed dose combination of atazanavir and cobicistat approved by FDA, has also been added.
- **Darunavir:** Dosing information has been added for adolescents 12 years of age and older weighing at least 30 kg with at least one darunavir-associated mutation.

Integrase Strand Transfer Inhibitors

- **Elvitegravir:** The section was updated to include information about the fixed dose combination, Genvoya, for use in persons aged ≥12 years and weighing at least 35 kg.

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Pharmacokinetic Enhancers

- **Cobicistat:** The section was updated to include information about the fixed dose combination, Genvoya, for use in persons aged ≥12 years and weighing at least 35 kg.

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Members of Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (Last updated March 1, 2016; last reviewed March 1, 2016)

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 HIV-Infected Children (the Panel) convened by the Office of AIDS Research Advisory Committee (OARAC) and supported by the National Resource Center at the François-Xavier Bagnoud Center (FXBC), Rutgers, The State University of New Jersey; the Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH).

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Special Thanks

We would like to acknowledge four members who are resigning from the Panel after many years of outstanding service and contributions: **Carolyn Burr, RN, EdD** (18 years); **Brian Feit, MPA** (13 years); **Eva Powell, BA** (4 years); and **Allan W. Taylor, MD, MPH** (4 years).

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HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children Financial Disclosure (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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Introduction (Last updated March 1, 2016; last reviewed March 1, 2016)

These updated Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents address the use of combination antiretroviral therapy (ART) for HIV-infected infants, children, and adolescents. In general, these guidelines are appropriate for the care and management of youth with sexual maturity rating (SMR, formerly Tanner staging) I-III, whereas the guidelines developed by the Panel on Antiretroviral Guidelines for Adults and Adolescents are suitable for the care and management of adolescents in late puberty (SMR IV-V). Guidance on management of adverse events associated with use of antiretroviral (ARV) drugs in children and a detailed review of information about safety, efficacy, and pharmacokinetics (PK) of ARV agents in children is also included. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (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 the prevention and treatment of opportunistic infections (OIs) in HIV-exposed and -infected children,[1] for the use of ARV agents in HIV-infected adolescents and adults,[2] for the use of ARV drugs in pregnant HIV-infected women,[3] and for the prevention and treatment of OIs in HIV-infected adults.[4] These guidelines are developed for the United States and may not be applicable in other countries. The World Health Organization (WHO) 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 HIV-infected children 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 reduce 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 burdens, and less frequent medication administration, all factors that can improve adherence and outcomes. The use of ARV drugs in HIV-infected pregnant women has resulted in a dramatic decrease (to less than 2%) in the rate of HIV transmission to infants in the United States. In addition to decreasing the number of infants with HIV infection, children in the United States who are HIV-infected 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 HIV-infected individuals, but unique considerations exist for HIV-infected infants, children, and adolescents, including:

- Acquisition of infection through perinatal exposure for most infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to ARV drugs in most perinatally infected children;
- 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 viral loads in perinatally-infected infants than in HIV-infected adolescents and adults;

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- Changes in PK parameters with age caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance;[12]
- 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 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 were available, unpublished data and the clinical expertise of the Panel members were also considered. The Panel intends for these guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.

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 HIV-infected infants, children, and adolescents (through puberty) 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 HIV-infected infants, children, and adolescents in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—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 representative of the François-Xavier Bagnoud Center 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.
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.

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

Topic	Comment
Other Guidelines	These guidelines focus on HIV-infected infants, children, and adolescents in early puberty (SMR I-III). For more detailed discussion of issues of treatment for adolescents in late puberty (SMR IV-V), the Panel defers to the expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of ART in HIV-infected pregnant women and interventions for prevention of perinatal transmission, ART for nonpregnant HIV-infected adults and postpubertal adolescents, 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.[13-15]

Studies relating activity of the drug-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

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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 HIV-infected adults and children 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 **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials in children[a] with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints plus accompanying data in children[a] from one or more well-designed, non randomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, non-randomized trials or observational cohort studies in children[a] with long-term clinical outcomes **II*:** One or more well-designed, non-randomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children[a] from one or more smaller non-randomized trials or cohort studies with clinical outcome data **III:** Expert opinion

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

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Identification of Perinatal HIV Exposure (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.
- 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 **(AIII)**.
- 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)**.
- 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.
- When acute 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)**.
- Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
- 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*

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

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

HIV Testing in Pregnancy

HIV infection should be identified prior to pregnancy 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 HIV-Infected Children (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:

- HIV-infected women 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]

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- 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 HIV-infected women about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce perinatal transmission of HIV;[4,11-13]
- Counseling of HIV-infected women about the risks of HIV transmission through breast milk (breastfeeding is not recommended for HIV-infected women 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 HIV-infected infants and in those HIV-exposed infants whose HIV infection status remains indeterminate;[15] and
- Early diagnostic evaluation of HIV-exposed infants, as well as testing of partners and other children, to permit prompt initiation of ART in infected individuals.[1,16,17]

Technological improvements have resulted in increased sensitivity for 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 HIV-infected pregnant woman 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 HIV-infected individuals, 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

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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.[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 found to be HIV-infected 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 HIV-exposed infants 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

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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 exposed-infant reporting regulations that may exist in their jurisdictions; this is in addition to mandatory reporting of HIV-infected persons, 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 March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- Virologic assays 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)**.
- HIV RNA and HIV DNA nucleic acid tests are recommended as preferred virologic assays **(AII)**.
- Virologic diagnostic testing at birth should be considered for HIV-exposed infants at high risk of perinatal HIV transmission **(AIII)**.
- Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:
  - 14 to 21 days **(AII)**
  - 1 to 2 months **(AII)** (preferably, 2 to 4 weeks after cessation of antiretroviral prophylaxis **[BIII]**)
  - 4 to 6 months **(AII)**.
- A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
- Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with 1 obtained at age ≥1 month and 1 at age ≥4 months, or 2 negative HIV antibody tests from separate specimens obtained at age ≥6 months **(AII)**.
- Some experts confirm the absence of HIV infection at 12 to 18 months of age in children with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.
- 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 a nucleic acid test (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations) **(AII)**.
- Diagnostic testing in children with non-perinatal exposure 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)**.

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

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 HIV-exposed infants by age 1 to 2 months and in virtually all infected infants 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 should 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]

HIV culture is not used for routine HIV diagnostic testing.[4] Antigen/antibody combination immunoassays (fourth- and fifth-generation tests) which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are also not recommended for infant diagnosis in the United States because the sensitivity and specificity of the assay in

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the first months of life are less than that of HIV virologic tests.[5-7]

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 HIV-exposed and undergo the HIV diagnostic testing described here[8] (see Infant Antiretroviral Prophylaxis in the Perinatal Guidelines for recommendations on infant antiretroviral [ARV] prophylaxis and management).

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in the plasma. Their specificity (for results ≥5,000 copies/mL) has been shown to be 100% at birth and at 1, 3, and 6 months of age and is comparable to HIV DNA PCR.[9] 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. 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 infected infants 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).[3,8-10]

While HIV DNA PCR remains positive in most individuals receiving ARV treatment, HIV RNA assays could potentially be affected by maternal antenatal treatment or infant combination ARV prophylaxis.[11] 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 receiving multidrug prophylaxis (n = 9) compared to levels among infected 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.[9] 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 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.[12-16]

HIV DNA Polymerase Chain Reaction

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 infected infants 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.[8-10,15]

Two studies provide data on diagnostic testing at different time points in HIV-infected infants 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 postpartum prophylaxis containing 6 weeks of zidovudine either alone or with 2 or 3 other ARVs; 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 infected infants were identified at birth. Overall, by 4 to 6 weeks of age, 89% of 140 infected infants were identified. Of the 47 infected infants who had negative DNA PCR tests at birth, 68% were identified during the period of

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neonatal ARV prophylaxis at 4 to 6 weeks; by 3 months, all 47 infants were identified.[17] 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 confirmed infected infants 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 infected 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 was 24.8 to 42.5 days.[18]

Although the AMPLICOR® HIV-1 DNA test has been widely used for diagnosis of infants born to HIV-1-infected mothers 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.

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.[19] In an evaluation of perinatally infected infants 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.[20] 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.[21] 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%.[22] 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. Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.[23-26] 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.[27-29]

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 more uncommon Group O strains, compared to older RNA assays that did not detect or properly quantify all non-B subtypes and Group O HIV[30-35] (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,

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Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and parts of India.[36,37] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions;[38,39] 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.[40,41]

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 HIV-2 infected 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., HIV-1 antibody-positive on an initial immunoassay test, repeatedly indeterminate results on HIV-1 Western blot, and HIV-1 RNA viral loads at or below the limit of detection).[42,43] 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 since this assay is not commercially available.[44-46] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[36,47]

Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

Virologic diagnostic testing should be considered at birth for HIV-exposed infants at high risk of perinatal HIV transmission. Virologic diagnostic testing should be performed for all HIV-exposed infants at age 14 to 21 days, at age 1 to 2 months (preferably 2 to 4 weeks after cessation of ARV prophylaxis), and at age 4 to 6 months.

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]) test at age ≥8 weeks, or one negative HIV antibody test at age ≥6 months.[1,8] *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.[48] 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 2 or more negative virologic tests (i.e., negative NATs [RNA or DNA]), one at age ≥1 month and one at age ≥4 months, or 2 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.

Virologic Testing at Birth (Optional)

Virologic testing at birth should be considered for newborns at high risk of perinatal HIV transmission, such as infants born to HIV-infected mothers who did not receive prenatal care or prenatal ARVs, were diagnosed with acute HIV infection during pregnancy, or who had HIV viral loads >1,000 copies/mL close to the time of delivery.[49-53] In one study, 66.4% of infected infants whose mothers had not received prenatal ARVs were identified at birth.[17] Prompt diagnosis is critical to allow for discontinuing ARV prophylaxis and instituting early ARV therapy (see When to Initiate Therapy). Blood samples from the umbilical cord should not be used

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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.[15,49,50]

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,[8] and early identification of infection would permit discontinuation of neonatal ARV prophylaxis and initiation of ARV therapy (see Infants Younger than Age 12 Months and Table 5 in When to Initiate Therapy).

Virologic Testing at Age 1 to 2 Months

Virologic diagnostic testing should be considered 2 to 4 weeks after cessation of ARV prophylaxis. In such situations, the test would be obtained at 6 weeks (in the case of 4 weeks of neonatal ARV prophylaxis) or at 2 months (in the case of 6 weeks of prophylaxis) (see Infant Antiretroviral Prophylaxis in the Perinatal Guidelines).[54,55] Although the use of antepartum, intrapartum, and neonatal zidovudine single-drug prophylaxis did not delay detection of HIV by culture in infants in Pediatric AIDS Clinical Trials Group protocol 076 or affect the sensitivity and predictive values of many virologic assays,[8] this may not always apply to current prenatal and neonatal ARV regimens if the test is obtained while the infant is receiving neonatal ARV prophylaxis.[9]

Testing performed at this age is intended to maximize the detection of HIV-infected infants.[9,56] 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 infected infants 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 infected infants in one study,[9] and 68% of infected infants in the second study.[17] 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.

An infant with 2 negative virologic tests—1 at age ≥14 days and 1 at age ≥4 weeks—or one 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

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

Antibody Testing at Age 6 Months and Older

Two or more negative HIV antibody tests performed in non-breastfed infants at age ≥6 months can also be used to **definitively** exclude HIV infection in HIV-exposed children with no clinical or virologic laboratory documented evidence of HIV infection.[57]

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.[58] Although the majority of HIV-uninfected infants 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.[58-61]

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Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion (≤24 Months)

Non-breastfed, perinatally HIV-exposed infants 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 infants are called late seroreverters).[58-61] In one study, 14% seroreverted after age 18 months.[58] 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 HIV-Exposed Children 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 HIV-exposed infants who had prior negative HIV virologic tests. This occurs in infants 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 between residual antibodies in uninfected, late-seroreverting children and 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.[27-29] The diagnostic approach in these situations is discussed above in the sections in Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and in Virologic Assays to Diagnose HIV-2 Infections.

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

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., among women from communities in which breastfeeding is the norm, women who fear that not breastfeeding would be a stigma, 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).[62-65] Donor breast milk from an unscreened HIV-infected donor is an additional potential risk factor. Infants who are breastfed by HIV-infected women 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 to rule out acquisition of HIV through breast milk will only be accurate after breastfeeding has completely ceased. Factors to consider in the choice of diagnostic tests in breastfed children 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 initial test (see Infant Antiretroviral Prophylaxis in the Perinatal Guidelines).[66,67]

Receipt of solid food premasticated or prechewed by an HIV-infected caregiver has been documented to be associated with risk of HIV transmission.[68-73] If this occurs in perinatally HIV-exposed infants 24 months or younger with prior negative virologic tests, it will be necessary for such children to undergo virologic

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diagnostic testing, as they may have residual maternal HIV antibody (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations).

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.[74]

Diagnosis of HIV-1 infection in children with non-perinatal exposure or children with perinatal exposure aged >24 months relies primarily on HIV antibody and antigen/antibody tests.[1] FDA-approved diagnostic tests include:

- Antigen/antibody combination immunoassays detect HIV-1/2 antibodies as well as HIV-1 p24 antigen (fourth and fifth generation tests [the fifth generation test, Bio-Rad BioPlex 2200 HIV, 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.
- HIV-1/2 immunoassays (third-generation antibody tests): Alternative for initial testing.
- HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies (Multispot HIV-1/HIV-2 test or Geenius™ HIV 1/2 Supplemental Assay): 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 that recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies (Multispot HIV-1/HIV-2 test or Geenius™ HIV 1/2 Supplemental Assay) 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.[1,75] 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).[44-46]

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).

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Clinical and Laboratory Monitoring of Pediatric HIV Infection

(Last updated March 1, 2016; last reviewed March 1, 2016)

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, monitoring should be at least every 3 to 4 months thereafter **(AIII)**.
- Antiretroviral 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 side 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 (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*)**.
- More frequent CD4 cell count and plasma viral load monitoring should be performed in 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 antiretroviral therapy 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*)**.
- 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 HIV-infected children 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 HIV-infected children, relevant to both those who are newly diagnosed and those who are receiving combination antiretroviral therapy (ART).

Clinical and Laboratory Monitoring of Children With HIV Infection

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 not started on ART after diagnosis, monitoring should be every 3 to 4 months thereafter (AIII).

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Antiretroviral 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 for HIV-associated conditions including anemia, leukopenia, thrombocytopenia, elevated glucose, transaminases, creatinine, hypoalbuminemia, and HIV-associated nephropathy (urinalysis). In addition, HIV-infected children should have a complete age-appropriate medical history and physical examination (see Table 3). Opportunistic infection monitoring should follow guidelines appropriate for the child's exposure history and clinical setting (see the Pediatric Opportunistic Infections Guidelines).

Laboratory confirmation of HIV infection should be obtained if available documentation is incomplete (see Diagnosis of HIV Infection). Genotypic resistance testing should be performed, even if ART is not initiated immediately. In addition, a full antiretroviral (ARV) drug history including exposure to 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 is positive (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information).

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 (NRTI)-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 associated with a particular ARV drug, see Tables 12a-12l in Management of Medication Toxicity or Intolerance.

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

After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical side 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 who start ART or who change to a new regimen should be followed to assess effectiveness, tolerability, and adverse effects 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

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adjust their schedules to allow for consistent and routine administration of medication doses. Children may also experience adverse effects 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 Combination Antiretroviral Therapy

Within 1 to 2 weeks of initiating therapy, children should be evaluated either in person or by phone to identify clinical adverse effects 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 Combination 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. Because of higher baseline viral load in infants and young children, the decline in viral load after ART initiation may be slower than in adults. 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*).

More frequent CD4 cell count and plasma viral load monitoring should be performed in 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 (e.g., evaluation of serum lactate in a child receiving NRTIs who develops symptoms consistent with lactic acidosis). 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 opportunistic infection 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.[1-6]

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

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

The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children 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 opportunistic infection 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 antiretroviral therapy 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).

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 <5 years of age (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 who are HIV-uninfected are considerably higher than values observed in uninfected adults (and slowly decline to adult values by age 5 years).[7,8] In children younger than age 5 years, the absolute CD4 cell count tends to vary more with age than does CD4 percentage. Therefore, in HIV-infected children younger than age 5 years, CD4 percentage has historically been preferred for monitoring immune status, whereas absolute CD4 cell count has been the preferred option for children aged ≥5 years.[9-11] A more recent 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.[12] Current pediatric HIV disease classification is based on absolute CD4 cell count.[13]

In HIV-infected children, as in infected adults, 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).

The prognostic value of CD4 cell count and percentage and plasma viral load was assessed in a large individual patient meta-analysis (HPPMCS), which incorporated clinical and laboratory data from 17 pediatric studies and included 3,941 HIV-infected children receiving either no therapy or only zidovudine monotherapy.[10] The

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analysis looked at the short-term (12-month) risk of developing AIDS or dying based on a child's age and selected values of CD4 cell count or percentage and plasma viral load at baseline (see Figures A and B and Table A in Appendix C: Supplemental Information). In a separate analysis of this dataset, predictive value of CD4 cell count for risk of death or AIDS/death in HIV-infected children aged 5 years or older was similar to that observed in young adults, with an increase in the risk of mortality when CD4 cell count fell below 350 cells/mm^3 (see Figure C and Table B in Appendix C: Supplemental Information).[9,14]

The risk of disease progression associated with a specific CD4 cell count or percentage varies with the age of the child. Infants in the first year of life experience higher risks of progression or death than older children for any given CD4 stratum. For example, comparing a 1-year-old child with a CD4 percentage of 25% to a 5-year-old child with the same CD4 percentage, there is an approximately fourfold increase in the risk of AIDS and sixfold increase in the risk of death in the 1-year-old child (see Figures A and B in Appendix C: Supplemental Information). Children aged ≥5 years have a lower risk of progression than younger children, with the increase in risk of AIDS or death corresponding to CD4 cell count more similar to those in young adults (see Figure C and Table B in Appendix C: Supplemental Information). In the HPPMCS, there were no deaths among children aged ≥5 years with CD4 cell count >350 cells/mm^3, although in younger children there continued to be a significant risk of death even with CD4 cell count >500 cells/mm^3 (see Table B 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, these risk profiles contribute to the level of urgency for recommendations on when to initiate therapy in a treatment-naive HIV-infected child (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).[10]

Measurement of CD4 cell count and percentage can be associated with considerable intrapatient variation.[11] 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 infected adults, 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 perinatally infected infants differs from that in infected adults and adolescents. High plasma viral load persists in untreated infected 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]

High plasma viral load in infants younger than 12 months has been correlated with disease progression and death, but the range of plasma viral loads overlaps considerably in young infants who have rapid disease progression and those who do not.[18,20] Plasma viral load >100,000 copies/mL in older children also has been associated with high risk of disease progression and mortality, particularly if CD4 percentage is <15% (see Table C in Appendix C: Supplemental Information).[22,23] The most robust data set available to elucidate the

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predictive value of plasma viral load for disease progression in children was assembled in the HPPMCS[10] (see Immunologic Monitoring in Children: General Considerations) in children on no therapy or only zidovudine monotherapy, which showed that the risk of clinical progression to AIDS or death dramatically increases when viral load exceeds 100,000 copies (5.0 $\log_{10}$ copies)/mL; at lower values, only younger children show much variation in risk (see Figures D and E and Table A in Appendix C: Supplemental Information). At any given viral load, infants younger than 1 year were at higher risk of progression than older children, although these differences were less striking than those observed for the CD4 percentage data.

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 HIV-infected children and adults, 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. Choice of HIV RNA assay, particularly for young children, may be influenced by the amount of blood required for the assay. The NucliSENS assay requires the least blood (100 microliters of plasma), followed by the RT-PCR assays such as the COBAS AmpliPrep/COBAS TaqMan (1,000 microliters of plasma) and VERSANT assays (500 microliters of plasma).

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 infected infants and young children. 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 HIV-infected adults than in HIV-infected children (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.

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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	√		√				√	
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 45 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 tenofovir disoproxil fumarate, more frequent urinalysis is considered.

[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 = combination 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)	$40–10^7$	$25–10^7$	$20–10^7$	$37–11x10^7$
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 March 1, 2016; last reviewed March 1, 2016)

General Considerations

Treatment of pediatric HIV infection has steadily improved since the introduction of potent combination antiretroviral (ARV) drug regimens that effectively suppress viral replication in most patients, resulting in a lower risk of virologic failure due to development of drug resistance. Antiretroviral therapy (ART) regimens including at least three drugs from at least two drug classes are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children.[1,2] In the United States and the United Kingdom, significant declines in morbidity, mortality, and hospitalizations have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of highly active combination regimens.[3-5] As a result, perinatally HIV-infected children are now living into the third and fourth decades of life, and likely beyond.

The increased survival of HIV-infected children 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[6-9] (see Management of Medication Toxicity or Intolerance).

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.[10-12] 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.

In addition to trials demonstrating benefits of ART in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,[13] a randomized clinical trial has provided evidence of benefit with initiation of ART in asymptomatic adults with CD4 cell counts >500 cells/mm^3.[14] 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 HIV-infected children than in adults, this Panel recommends ART for all HIV-infected children, with differing strengths of recommendation based on age and CD4 cell counts (see When 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 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), and level of HIV plasma viremia;
- Availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child's age/weight group;
- Potency, complexity (e.g., dosing frequency, food and fluid 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;

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- 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 HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children 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 perinatally infected infants, due to persistence of HIV in CD4 lymphocytes and other cells.[15-17] This was demonstrated when an HIV-infected child treated with ART at 30 hours of age suffered viremic rebound after more than 2 years of undetectable HIV RNA levels while off ART.[18,19] Some data suggest that the half-life of intracellular HIV proviral DNA is even longer in infected children than in adults (median 14 months vs. 5–10 months, respectively).[20] 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 HIV-infected children and adolescents include:

- Preventing and reducing HIV-related morbidity and mortality;
- Restoring and/or preserving immune function as reflected by CD4 cell measures;
- Maximally and durably suppressing viral replication;
- Preventing emergence of viral drug-resistance mutations;
- Minimizing drug-related toxicity;
- Maintaining normal physical growth and neurocognitive development;
- Improving quality of life;
- Reducing the risk of sexual transmission to discordant partners in adolescents who are sexually active; and
- Reducing the risk of perinatal transmission in adolescent females who become pregnant.

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

Use and Selection of Antiretroviral Therapy

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

Drug Sequencing and Preservation of Future Treatment Option

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

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Maximizing Adherence

As discussed in Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents, 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. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with a child's caregiver and the child (when age appropriate) before therapy is initiated. Potential problems should be identified and resolved before starting therapy, generally even if this delays initiation of therapy. 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 March 1, 2016; last reviewed March 1, 2016)

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 Antiretroviral Guidelines for Adults and Adolescents). 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 HIV-infected adults (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 HIV-infected adults 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 HIV-Infected Children recommends treatment for all HIV-infected children. However, the strength of the recommendation 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 HIV-infected children than in adults. 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, as demonstrated by the lack of clinical benefit of immediate ART observed in the PREDICT trial, which enrolled children aged >1 year (median age 6.4 years), and the risk of progression was extremely low in both groups.[5] Concerns about adherence and toxicities become particularly important when therapy in children is initiated at a young age and will likely be life-long.

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 quasispecies. Initiation of therapy at higher CD4 cell counts has been associated with fewer drug resistance mutations at virologic failure in adults.[6] Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression.[7,8] 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.[7,9-11] 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.

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Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive, HIV-Infected Infants and Children

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	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[e] **(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 postpubertal adolescents

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

[a] For infants ≤2 weeks, see Specific Issues in Antiretroviral Therapy for Neonates

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

[c] Table 6

[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.

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 percentage (>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.[12] 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

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recommends initiating therapy for all infants <12 months regardless of clinical status, CD4 percentage, or viral load (Box Recommendations). Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with an HIV-infected infant's caregivers. However, given the high risk of disease progression and mortality in young HIV-infected infants, it is important to expedite this assessment in infants younger than 12 months.

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 infected infants; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[13] 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.[14] 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.[14]

Identification of HIV infection during the first few months of life permits clinicians to initiate ART during the initial phases of primary infection. Data from a number of observational studies in the United States and Europe suggest that infants who receive early treatment are less likely to progress to AIDS or death than those who start therapy later.[7,15,16] A study of 195 South African children initiating ART aged <24 months found that infants treated by 6 months achieved target growth milestones more rapidly than children who initiated therapy between 12 and 24 months.[17] Several small studies have demonstrated that, despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.[18,19] In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication.[20] Some of these infants have become HIV seronegative. Although there is a single case report of a period of remission in an HIV-infected child, discussed below, current ART has not been shown to eradicate HIV infection in perinatally infected infants because of persistence of HIV in CD4 lymphocytes and other cells.[21-23]

The report of a prolonged remission in an HIV-infected child in Mississippi generated discussion about early initiation of ART in newborn infants with high-risk HIV exposure. This newborn, born to a mother who did not receive antenatal or perinatal ART, was treated with a three-drug ART regimen at 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.[24,25] 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, drug and dose selection in this age group is challenging (see What to Start and Specific Issues in Antiretroviral Treatment for Neonates). 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.[26,27] 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 HIV-infected infants initiating therapy at <12 months.[7,28,29] In a 5-year follow-up study of 40 HIV-infected children 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.[7] More rapid viral suppression in young infants may also be important in reducing the long-lived HIV reservoir; a study of 17 HIV-infected infants initiating ritonavir-boosted lopinavir-based ART before 6 months demonstrated that time to the first HIV viral load <400 copies/mL was correlated with the size of the long-lived HIV reservoir (i.e., the resting memory CD4

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cell pool).[30] In addition, in the Pediatric HIV/AIDS Cohort Study/Adolescent Master Protocol (a cross-sectional study of 144 perinatally infected youth 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 peripheral blood mononuclear cells, respectively).[31]

Information on appropriate drug dosing in infants younger than 3 to 6 months is limited. 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.[32] When drug concentrations are subtherapeutic, 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.[33]

Children Aged 1 Year and Older

In general, disease progression is less rapid in children aged ≥1 year.[13] However, children with 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.[34] In these children, 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[35] published a review on the effectiveness of ART in HIV-infected children aged <2 years based on data from published randomized trials of early versus deferred ART.[4,36] The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that data are 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) trial was designed to investigate the impact on AIDS-free survival and neurodevelopment of deferral of ART in children aged >1 year.[37] This multicenter, open-label trial randomized 300 HIV-infected children aged >1 year (median 6.4 years) to immediate initiation of ART or deferral until the CD4 percentage was <15%. The median baseline CD4 percentage was 19% (IQR 16% to 22%) and 46% of children in the deferred group started ART during the study. 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 two groups. 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 children, the prognostic significance of a specific CD4 percentage or count varies with age.[14,38] In data from the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count in children aged 1 to 4 years than in children aged ≥5 years (see Figures A and B and Tables A and B in Appendix C: Supplemental Information). Data from the HIV Paediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful

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prognostic marker for disease progression in children aged ≥5 years, with risk of progression similar to that observed in adults (see Table B in Appendix C: Supplemental Information).[14,39] For children aged 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (see Table A in Appendix C: Supplemental Information).

Because the CD4 percentage is more consistent than the naturally declining CD4 cell count in the first years of life, it has been used preferentially to monitor immunologic status in children aged <5 years. However, an analysis of more than 21,000 pairs of CD4 measurements from 3,345 children aged <1 to 16 years in the HIV Paediatric Prognostic Markers Collaborative Study found that CD4 cell counts provide greater prognostic value over CD4 percentage for short-term disease progression for children aged <5 years as well as in older children.[40] For example, the estimated hazard ratio for AIDS or death at the 10th centile of CD4 cell count (compared with the 50th centile) was 2.2 (95% confidence interval [CI]) 1.4, 3.0) for children aged 1 to 2 years versus 1.2 (CI 0.8, 1.6) for CD4 percentage. The CDC has issued an updated HIV infection staging classification based on age-specific CD4 values, indicating a preference for CD4 count over CD4 percentage in all ages (see Revised Surveillance Case Definition for HIV Infection at http://www.cdc.gov/mmwr/pdf/rr/rr6303.pdf and Table 5).

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count.[38] Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality[41-43] and lower neurocognitive performance;[44] similar findings have been reported in adults.[45-47] Similarly, in the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children aged >1 year when HIV RNA levels were ≥100,000 copies/mL (see Figures D and E and Table A in Appendix C: Supplemental Information).[38] For example, the estimated 1-year risk of death was 2 to 3 times higher in children with plasma HIV RNA 100,000 copies/mL compared with 10,000 copies/mL and 8 to 10 times higher with plasma HIV RNA >1,000,000 copies/mL.

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.[48-52] A secondary analysis of PENPACT-1 (Pediatric AIDS Clinical Trials Group 390/Paediatric European Network for Treatment of AIDS 9) evaluated population-level impacts of ART initiation at different CD4 percentages and age thresholds on CD4 percentage recovery.[53] PENPACT-1 was a multicenter, Phase 2/3 randomized, open-label trial enrolling ART-naive children aged >30 days to <18 years from Europe, North America, and South America. The primary aims were to compare a protease inhibitor- or non-nucleoside reverse transcriptase inhibitor-based ART regimen for initial therapy and evaluate viral load thresholds for switching from first-line to second-line ART. Because no significant differences were found among randomized arms, participants were pooled across arms to study CD4 responses. Two hundred and sixty-six children were enrolled, and 162 had at least "mild" immunosuppression at enrollment using World Health Organization (WHO) 2007 criteria; this group was evaluated for CD4 percentage recovery to ≥10% for age within 4 years of initiating ART. CD4 percentage recovery was significantly associated with WHO-staged baseline CD4 percentage, with 97% (95% CI: 85%–99%) of those with "mild" immunodeficiency (n = 31) and 87% (95% CI: 62%–87%) of those with "advanced" immunodeficiency (n = 40) ever having a normal CD4 value within 4 years of ART initiation vs. 60% (95% CI 48–68%) among those with "severe" immunodeficiency (n = 91) ($P < 0.001$). When baseline CD4 percentage and age effects were combined, >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 perinatally infected children 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.[54] Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.[17,54,55] Older age at ART initiation (median age 9.4 years; range 5.2–17.6 years) was associated with delayed onset of puberty and all Tanner stages ($P < 0.05$) and menarche ($P = 0.02$) in Ugandan and Zimbabwean HIV-infected children in the ARROW trial.[56]

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Finally, the PREDICT Study demonstrated improved height z-scores in the early treatment arm compared with no improvement in the deferred arm.[37] These combined data suggest that initiation of ART at higher CD4 values and younger ages maximizes the potential benefit for immunologic recovery.

Given that disease progression in children aged ≥5 years is similar to that in adults,[39] and the START clinical trial demonstrated reduction in morbidity and mortality with initiation of ART when the CD4 cell count is >500 cells/mm^3 (INSIGHT START),[57,58] most experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. While the DHHS Adult Treatment Guidelines Panel has moved to endorse initiating ART in all HIV-infected adults regardless of CD4 cell count,[59] one component of their rationale is the compelling data demonstrating that ART is effective in preventing secondary transmission of HIV. However, prevention of sexual transmission of HIV is not a significant consideration for children aged <13 years. 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, e.g., bone, cardiac, mitochondrial and/or other metabolic toxicities, are not yet available. Some studies have shown that a small proportion of perinatally infected children may be long-term nonprogressors, with no immunologic or clinical progression by age 10 years despite receiving no ART.[60-62] Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in childhood is often challenging.[63] 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 perinatally infected children during adolescence.[64] The relative benefits of initiating ART in asymptomatic children with low viral burdens and high CD4 cell counts in general outweigh these potential risks.

The Panel has used these data to formulate recommendations on 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.

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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 (page 1 of 2)

Mild HIV-Related Symptoms
Children with two or more of the conditions listed but none of the conditions listed in Moderate Symptoms category • Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • 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 × 109/L]), and/or thrombocytopenia (platelet count <100 × 103/µL [<100 × 109/L]) persisting for ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children older than age 6 months • Cardiomyopathy • Cytomegalovirus infection, with onset before 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month • Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex • Nephropathy • Nocardiosis • Persistent fever (lasting >1 month) • Toxoplasmosis, onset before 1 month • Varicella, disseminated (complicated chickenpox)

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Table 6: HIV-Related Symptoms (page 2 of 2)

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

[a] Only among children aged <6 years.

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

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

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

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 March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations
• Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**. • For treatment-naive children, the Panel recommends initiating antiretroviral therapy with three 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. • Table 7 provides a list of Panel-recommended regimens that are "Preferred," "Alternative" or for "Use in Special Circumstances;" recommendations vary by age, weight, and sexual maturity rating. • For infants aged <42 weeks postmenstrual or <14 days postnatal, data are currently inadequate to provide recommended dosing to allow the formulation of an effective, complete antiretroviral therapy regimen (see Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection). • Emtricitabine, lamivudine, and tenofovir disoproxil fumarate have antiviral activity and efficacy against hepatitis B. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, the reader should access the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Criteria Used for Recommendations

In general, the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (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;

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- 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 *Alternatives* 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.
- *Use in 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 two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) plus one active drug from the following classes: non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) boosted with ritonavir, or integrase strand transfer inhibitor (INSTI). Choice of a regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Table 8. 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.

Choosing Among an Integrase Strand Transfer Inhibitor-Based, a Non-Nucleoside Reverse Transcriptase Inhibitor-Based, 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 adverse events (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 HIV-infected 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 rito LPV/r regimen after achieving virologic control.[2]

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- PENPACT-1 (PENTA 9/PACTG 390) compared a PI-based regimen and a NNRTI-based regimen in HIV-infected 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 ritona 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 efficacy, tolerability and fewer drug-drug interactions in adult comparative trials showing superiority of INSTI-containing compared to PI-containing and NNRTI-containing regimens[5-7] and small studies in ART-naive adolescents.[8]

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

- <2 years: LPV/r
- ≥2 years to <3 years: LPV/r or raltegravir
- ≥3 to 12 years: efavirenz, raltegravir, boosted atazanavir, or twice-daily boosted darunavir
- ≥12 years who have not reached sexual maturity: dolutegravir, elvitegravir/cobicistat (only the elvitegravir/cobicistat-containing fixed drug combination elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) (i.e., Genvoya) is recommended at this time), boosted atazanavir, or once-daily boosted darunavir

Alternative regimens are shown in Table 7.

Integrase Strand Transfer Inhibitor-Based Regimens (Integrase Strand Transfer Inhibitor plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone)

Summary: Integrase Strand Transfer Inhibitor-Based Regimens

Three INSTIs—dolutegravir, elvitegravir and raltegravir—are licensed for the treatment of ARV-naive HIV-infected adults. 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 HIV-infected children as young as age 4 weeks. Dolutegravir is approved for use in adolescents aged ≥12 years and studies in younger children are under way. Elvitegravir has been studied in adolescents in two, fixed-dose combination regimens and in combination with two NRTIs and ritonavir boosting. At this time, only one fixed-dose combination has sufficient experience in adolescents to recommend (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 aged ≥12 years and weighing ≥40 kg. The approval was supported by data from a study of 23 treatment-experienced—but INSTI-naive—adolescents.[8] The drug has a very favorable safety profile and can be dosed once daily in treatment of INSTI-naive patients.

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Efficacy in Clinical Trials:

- Dolutegravir was non-inferior to raltegravir for viral suppression to <50 copies/mL. Both were administered with two NRTI combinations in the SPRING-2 trial.[5]
- When dolutegravir in combination with abacavir and lamivudine was compared to efavirenz combined with tenofovir disoproxil fumarate (TDF) and emtricitabine, dolutegravir was superior to the efavirenz combination at week 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.[7,9]
- Similar findings were noted when a dolutegravir ART regimen was compared to a darunavir/ritonavir (DRV/r) ART regimen in the FLAMINGO study. The dolutegravir regimen was found to be superior at weeks 48 and 96, mostly due to drug discontinuation in the DRV/r study arm.[6,10]
- Twenty-three adolescents were enrolled and 22 (96%) completed the 48-week study visit of a safety, pharmacokinetics and efficacy study of dolutegravir in combination with two NRTIs. Dolutegravir was administered at weight-based fixed dosages of approximately 1 mg/kg. PK parameters were within the study targets based on adult PK ranges. At week 48, 74% (95% CI: 52% to 90%) had HIV RNA <400 copies/mL and 61% (95% CI: 39% to 80%) had levels <50 copies/mL. Dolutegravir was well tolerated.[8]

Adverse Events:

- Dolutegravir is well tolerated in adults and adolescents. In adult trials, insomnia and headache were the only AEs reported with an incidence of ≥2%. In the small number of adolescents studied, there were no reported AEs attributed to dolutegravir.[8]

Other Factors and Considerations:

- There are few drug interactions with dolutegravir.
- Dolutegravir is dosed once daily and is available in a single-tablet regimen.

Recommendations:

- Based on virologic potency and safety profile in adult and pediatric studies, the Panel recommends dolutegravir in combination with a two-NRTI backbone as a **Preferred INSTI** regimen for **adolescents aged ≥12 years and weighing ≥40 kg (AI*)**.

Elvitegravir

Elvitegravir is an INSTI available as a tablet, as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TDF (Stribild), and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TAF. Both are FDA-approved for use as ART in HIV-1-infected ART-naive adults. 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.

Efficacy in Clinical Trials:

- At 144 weeks, a combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be non-inferior to a regimen of efavirenz/emtricitabineTDF[11] and to a regimen of atazanavir/ritonavir (ATV/r) with emtricitabine/TDF.[12]
- 1,733 adults (in 2 studies) were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TDF. 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 bone mineral density (BMD) at spine (mean % change −1.30 vs. –2.86; $P < 0.0001$) and hip (−0.66 vs. –2.95; $P < 0.0001$).[13]

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- In a small study (14 participants) of elvitegravir/cobicistat/emtricitabine/TDF in treatment-naive adolescents (aged 12 to 17 years) therapy was well tolerated, steady state exposure was similar to adults and at 24 weeks, all subjects had viral loads <400 copies/mL and 11 had viral loads <50 copies/mL.[14]
- Elvitegravir/cobicistat/emtricitabine/TAF was studied in 49 ART-naive adolescents aged ≥12 years and weighing ≥35 kg and demonstrated similar PK parameters of the combination in adults, was well-tolerated and, at week 24, all subjects had viral loads <50 copies/mL.[15]

Adverse Events:

- In adult and adolescents, the most common AEs were diarrhea, nausea, and upper respiratory infection.[11,12,14,15]

Other Factors and Considerations:

- Because cobicistat inhibits CYP3A, drug-drug interactions may occur.
- Cobicistat inhibits the tubular secretion of creatinine resulting in a higher serum creatinine and a reduced estimated creatinine clearance without reducing glomerular function.
- Elvitegravir is dosed once daily.
- Elvitegravir tablets must be taken in combination with a ritonavir-boosted PI.

Recommendations:

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

Raltegravir

Raltegravir is FDA-approved for treatment of HIV-infected 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.

Efficacy in Clinical Trials:

- Raltegravir has been evaluated in three large randomized clinical trials (RCTs) 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.[16-18] 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.[19]
- Raltegravir has been studied in infants, children and adolescents in an open-label trial, IMPAACT P1066, to evaluate PK, safety, tolerability, and efficacy. In children and adolescents (96 treated at final dose of raltegravir), aged 2 through 18 years, who were mostly drug-experienced, 79.1% of the patients achieved a favorable viral load (HIV viral load <400 copies/mL or ≥1 $\log_{10}$ decline in viral load). 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.[20-22]

Adverse Events:

- Raltegravir has a favorable safety profile.
- In P1066, drug-related adverse AEs included one child each with psychomotor hyperactivity and insomnia, rash, and elevated transaminases.

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Other Factors and Considerations:

- Raltegravir lacks significant drug interactions.
- The availability of a tablet, chewable tablet, and powder formulations offers multiple options for administration. The tablet formulations are not interchangeable (they are not bioequivalent), and therefore, require different dosing.
- Twice-daily administration is necessary.

Recommendations:

- Based on RCTs in adults and pediatric studies, largely in ARV-experienced children and adolescents, the Panel recommends raltegravir as a **Preferred INSTI** in children **aged ≥2 years through 12 years** who are able to take either the chewable or film-coated tablets.
- 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 (Non-Nucleoside Reverse Transcriptase Inhibitor plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone)

Summary

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 HIV-infected adults. 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 two NRTIs is the preferred NNRTI for initial therapy of children aged ≥3 to 12 years based on clinical trial experience in adults and children.

Efficacy in Clinical Trials:

In clinical trials in HIV-infected adults and children, efavirenz in combination with two NRTIs has been associated with excellent virologic response.

- Efavirenz-based regimens have proven virologically superior or non-inferior to a variety of regimens including those containing LPV/r, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.[16,23-29]
- In the SINGLE trial in adults, dolutegravir in combination with abacavir and lamivudine was superior to efavirenz combined with TDF and emtricitabine at weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.[7,9]
- Efavirenz in combination with two NRTIs or with a NRTI and a PI has been studied in HIV-infected children[30-36] with results comparable to those seen in adults.

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Adverse Events:

- The major limitation of efavirenz is central nervous system (CNS) side effects including fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some, the symptoms may persist.
- The incidence of CNS AEs was correlated with efavirenz plasma concentrations.[37-40]
- 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.[41,42]
- Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than in adults.[34,36]

Other Factors and Considerations:

- Efavirenz capsules can be opened and sprinkled on age-appropriate food for use in children as young as age 3 months who weigh at least 3.5 kg.[43]
- Because of concerns regarding variable PK of the drug in the very young, the committee does not currently endorse its use for infants and children aged 3 months to 3 years.
- Although emerging information about the use of efavirenz in pregnancy is reassuring,[44-47] alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception, because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health **(BIII)**.

Recommendation:

- Based on efficacy and tolerability, the Panel recommends efavirenz in combination with a two-NRTI backbone as the **Preferred NNRTI** regimen for initial therapy of HIV infection in **children aged ≥3 to 12 years (AI*)** and is recommended as an **Alternative NNRTI** regimen for those aged **≥12 years who are not sexually mature** (Sexual Maturity Rating [SMR] I–III).

Nevirapine

Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens.[1,3,4,48-52]

Efficacy in Clinical Trials:

- RCTs in adults have not demonstrated virologic inferiority for a nevirapine-based regimen compared to either efavirenz or atazanavir-based regimens.[53,54]
- Randomized clinical trials in children have demonstrated conflicting results (see Choice of NNRTI- versus PI-Based Initial Regimens). P1060 demonstrated superiority of LPV/r over nevirapine in children aged <3 years as have observational studies. PENPACT-1 and PROMOTE-pediatrics allowed nevirapine or efavirenz and showed no difference between an NNRTI-based and PI-based regimen but both enrolled older children.[1,3,4,52,55-57]

Adverse Events:

- Adult randomized clinical trials have demonstrated higher rates of toxicity and drug discontinuation in the nevirapine arms compared to efavirenz or ATV/r.[53,54]
- Symptomatic hepatic toxicity is more frequent in individuals with CD4 cell counts at nevirapine initiation (women with CD4 cell counts >250 cells/mm^3 and men with CD4 cell counts >400 cells/mm^3). Hepatic toxicity appears to be less frequent in children than in adults but was reported to occur at a

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greater frequency among children with CD4 percentage ≥15% at therapy initiation.[50,51,58-60]

- The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown. Efavirenz use in this situation has been well tolerated in the very limited number of patients in whom it has been reported, but that substitution should be attempted with caution.[61]

Other Factors and Considerations:

- In the United States, nevirapine is the only NNRTI available in liquid formulation.
- Nevirapine also should be used with caution in children with elevated pretreatment liver function tests.

Recommendation:

- Based on the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare but potentially life-threatening hepatitis,[62,63] and conflicting data about virologic efficacy compared to preferred regimens, the Panel recommends nevirapine in combination with a two-NRTI backbone as an **Alternative NNRTI** regimen for **children aged >14 days to < 3 years (AI)**.

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.

Efficacy in Clinical Trials:

- A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be non-inferior to efavirenz. Subjects with pretreatment HIV viral loads ≥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.[27,64-66]
- A study of rilpivirine, 25 mg daily in combination with 2 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.[67,68]

Adverse Events:

- Rilpivirine is generally well tolerated. In studies in adults, neurologic events were most common and included insomnia, headache, dizziness and abnormal dreams or nightmares. There were fewer drug discontinuations related to rilpivirine compared to efavirenz.
- Somnolence and nausea were the AEs reported to be associated with rilpivirine in the adolescent study. Five and 2 of 36 patients reported somnolence and nausea, respectively.
- Depressive disorders were also reported in 7 of 36 subjects of which 2 of 36 were of Grade 3 or 4.

Other Factors and Considerations:

- Current FDA approval for rilpivirine in the adolescent population is only for the single-drug formulation.

Recommendation:

- Based on the limited experience in adolescents and larger body of evidence in adults, the Panel recommends rilpivirine in combination with a two-NRTI backbone as an **Alternative NNRTI** regimen for **adolescents aged ≥12 years and with HIV viral load ≤ 100,000 copies/mL (AI*)**.

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Protease Inhibitor-Based Regimens (Boosted Protease Inhibitors plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone)

Summary: 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 (CYP3A4) 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, two agents must be administered. In addition, the use of ritonavir boosting increases the potential for hyperlipidemia[69] and drug-drug interactions.

Preferred and alternative PIs are presented in alphabetical order below.

Atazanavir Boosted with Ritonavir

Atazanavir is a once daily PI that was approved by the FDA in March 2008 for use in combination with a two-NRTI backbone in children aged ≥6 years. 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.

Efficacy in Clinical Trials:

- ATV/r has efficacy equivalent to efavirenz-based and LPV/r-based combination therapy when given in combination with two NRTIs in treatment-naive adults.[23,70-72] In ACTG A5257, ATV/r was compared to DRV/r or the INSTI 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 (GI) complaints.[19]
- P1020 enrolled 195 HIV-infected ART-naive and ART-experienced patients 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.[73-75]
- Atazanavir in a powder formulation administered once daily boosted with liquid ritonavir was studied in infants and children aged ≥3 months and weighing ≥10 kg in two open-label clinical trials, PRINCE I and PRINCE II.[76] Sixty-five infants and children weighing between 10 and 25 kg were studied. Using a weight-band approach for determining dose, PK targets were met. The drug was well tolerated and among 41 naive infants and children, 27 (66%) achieved HIV RNA levels <50 copies at week 48.

Adverse Events:

- The main adverse effect associated with ATV/r is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations.

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- Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher with ritonavir boosting than with atazanavir alone.[69]

Other Factors and Considerations:

- Atazanavir is available in a powder and capsule formulations administered once daily.
- Atazanavir is not coformulated with ritonavir so liquid or tablet ritonavir must also be given.
- Atazanavir co-formulated with cobicistat is FDA-approved for adults but has not been studied in children.

Recommendations:

- Based on virologic potency in adult and pediatric studies and tolerability in pediatric studies, the Panel recommends atazanavir capsules boosted with ritonavir in combination with a two-NRTI backbone as a **Preferred PI regimen for children aged ≥3 years (AI*)**.
- Because of the limited experience with atazanavir boosted with ritonavir in younger children, the Panel recommends atazanavir boosted with ritonavir 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 Boosted with Ritonavir

Darunavir boosted with ritonavir is FDA-approved for ARV-naive and ARV-experienced adults and for ARV-naive and ARV-experienced children aged ≥3 years.

Efficacy in Clinical Trials:

- In a randomized, open-label trial in adults, DRV/r (800/100 mg once daily) was compared to LPV/r (once or twice daily) when both boosted PIs were administered in combination with TDF fumarate/emtricitabine. DRV/r was found to be non-inferior at week 48 and superior at week 192. AEs were also less common in the DRV/r group ($P < 0.01$).[77,78]
- DRV/r was compared to dolutegravir, both in combination with a two-NRTI backbone, in the FLAMINGO study. The rate of virologic suppression was greater with dolutegravir mainly due to more drug discontinuation in the DRV/r treatment arm.[10]
- ART with DRV/r, ATV/r and raltegravir showed similar virologic suppression in the ACTG A5257 study.[19]
- To date the only clinical trial of darunavir boosted with ritonavir as initial therapy in pediatric patients is the DIONE study of once-daily DRV/r in treatment-naive adolescents aged 12 to 18 years (mean age, 14.6 years). After 24 weeks of treatment, 11 of 12 subjects had HIV-1 RNA <50 copies/mL and the agents were well tolerated.[79]
- In a study of treatment-experienced children (aged 6–17 years), DELPHI, twice daily DRV/r-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks.[80]
- In a study of treatment-experienced pediatric participants (aged 3 to <6 years and weighing ≥10 kg to <20 kg), ARIEL, 57% of subjects had HIV-1 RNA <50 copies/mL and 81% < 400 copies/mL after 24 weeks of treatment with twice daily DRV/r.[81]

Adverse Events:

- DRV/r is generally well tolerated in children and adolescents with the most commonly reported AEs being vomiting, diarrhea, abdominal pain, rash and headache.

Other Factors and Considerations:

- Darunavir is available as an oral suspension and tablet.

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- Because of available pill sizes and twice-daily administration in young children, regimens may be complicated by multiple pills and different pill strengths.
- DRV/r is approved for once-daily use in adults and children. A PK study of 24 patients, aged 14 to 23 years receiving once-daily DRV/r demonstrated darunavir exposure similar to that in adults receiving once-daily therapy. There was, however, a trend toward lower exposures in those aged <18 years.[82]
- In the ARIEL study, 10 treatment-experienced children were switched from twice-daily dosing to once-daily dosing after 24 weeks of therapy. PK studies were performed after 2 weeks of once-daily dosing and demonstrated darunavir mean AUC 24-hour equivalent to 128% of the adult AUC 24 hour.[83]

Recommendations:

- 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, the Panel recommends darunavir boosted with ritonavir in combination with a two-NRTI backbone as a **Preferred PI regimen for children aged ≥3 years and adolescents (AI*)**.
  - **Once-daily dosing** of DRV/r is part of a **Preferred PI regimen in treatment-naive adolescents aged >12 years (AI*)** based on findings from the DIONE study.
  - **Twice daily dosing** of DRV/r is part of a **Preferred PI regimen in children aged ≥3 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 Boosted with Ritonavir

Lopinavir boosted with ritonavir 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.

Efficacy in Clinical Trials:

- 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).[25,70,72,77,84-88]
- LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and low toxicity.[52,89-95]

Adverse Events:

- In adults, LPV/r 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).
- Post-marketing reports of LPV/r-associated cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported, predominantly in preterm neonates. These reports have resulted in a change in LPV/r labeling including a recommendation to not administer the combination to neonates until they reach a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

Other Factors and Considerations:

- LPV/r is available coformulated as a capsule and an oral solution.
- Dosing and efficacy data are available in infants as young as age 25 days.[93,96]
- Once-daily LPV/r is FDA-approved for initial therapy in adults,[97] but PK data in children do not support a recommendation for once-daily dosing.[98-100]

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Recommendations:

- Based on virologic potency in adult and pediatric studies and tolerability in pediatric studies, the Panel recommends LPV/r in combination with a two-NRTI backbone as a **Preferred PI regimen for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days to <12 years (AI)**.

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

Summary: Selection of Dual-Nucleoside Reverse Transcriptase Inhibitor Backbone Regimen

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, seven NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, and TDF) 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; and TDF in combination with lamivudine or emtricitabine.[32,73,101-105] 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.[106,107]

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.

Efficacy in Clinical Trials:

- Abacavir in combination with lamivudine has been shown to be as potent as or possibly more potent than zidovudine in combination with lamivudine in both children and adults.[108,109]
- Abacavir in combination with lamivudine has been compared to TDF with emtricitabine in several adult studies and meta-analyses with variable results.[110-113]
- Retrospective observational data from African children aged <16 years suggests the possibility of worse virologic outcome with abacavir/lamivudine-based first-line ART when compared to stavudine/lamivudine-based first-line ART.[114,115] Multiple confounders could have contributed to these findings and further data collection and evaluation is warranted.
- Abacavir combined with lamivudine was compared to zidovudine 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.[116]

Adverse Events:

- Abacavir-associated life-threatening HSRs occur in a small proportion of patients. HSRs are more common in individuals with certain HLA genotypes, particularly HLA-B*5701. Before initiating

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abacavir-based therapy in HIV-infected children, genetic screening for HLA-B*5701 should be performed and children who test positive for HLA-B*5701 should not receive abacavir **(AII*)**.

Other Factors and Considerations:

- Abacavir can be administered once daily in patients who are able to tolerate pill formulation of abacavir or abacavir-containing fixed-dose combination tablets.
- Infants and young children who initiate abacavir therapy with the liquid formulation should receive twice-daily abacavir. In children with undetectable plasma RNA after approximately 24 weeks of abacavir therapy, the change to once-daily administration, with appropriate dose modification, can be made.[117-120]

Recommendations:

- Based on virologic efficacy and favorable toxicity profile, 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, based on response, after approximately 24 weeks of dosing.

Tenofovir Alafenamide in Combination with Emtricitabine

TAF is an oral prodrug of tenofovir. It has recently been approved by the FDA as a component of the fixed-drug combination tablet also containing elvitegravir, cobicistat, and emtricitabine for the treatment of HIV infection in ARV-naive individuals aged ≥12 years with estimated creatinine clearance ≥30 mL/min.

Efficacy in Clinical Trials:

- In 2 studies, 1,733 adults were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TAF or elvitegravir/cobicistat/emtricitabine/TDF. 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 % change −3 vs. 20; $P < 0.0001$), and a significantly smaller decrease in BMD at the spine (mean % change −1.30 vs. –2.86; $P < 0.0001$) and hip (−0.66 vs. –2.95; $P < 0.0001$).[13]
- Elvitegravir/cobicistat/emtricitabine/TAF was studied in 49 ART-naive 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.[15]

Adverse Effects:

- Compared to TDF, which readily converts to tenofovir in the plasma, TAF remains stable in the plasma resulting in lower plasma and higher intracellular concentrations of tenofovir. TAF has fewer renal and bone AEs than does TDF.
- TAF has increased serum lipid levels compared with TDF in adolescents and adults.

Other Factors and Considerations:

- TAF is only available as a component of the fixed-drug combination of elvitegravir/cobicistat/emtricitabine/TAF.
- There is limited information about the long-term efficacy and safety of TAF.

Recommendations:

- Based on the potential for less renal and bone AEs, the Panel recommends TAF plus emtricitabine (combined with elvitegravir and cobicistat) as a **Recommended dual-NRTI combination in adolescents aged ≥12 years with estimated creatinine clearance ≥30 mL/min**.

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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.

Efficacy in Clinical Trials:

- In comparative clinical trials in adults, TDF when used with lamivudine or emtricitabine as a dual-NRTI backbone was superior to zidovudine used with lamivudine and efavirenz in viral efficacy.[121,122]
- TDF with emtricitabine has been compared to abacavir in combination with lamivudine in several adult studies and meta-analyses with variable results.[110–113]
- TDF has been studied in HIV-infected children in combination with other NRTIs and has efficacy similar to zidovudine or stavudine.[102-105]

Adverse Effects:

- In some but not all studies, decreases in BMD have been observed in both adults and children taking TDF for 48 weeks.[102-105,123,124] The clinical significance of these changes is not yet known.
- Renal toxicity has been reported in children receiving TDF.[125-128] Numerous drug-drug interactions with TDF and other ARV drugs, including didanosine, LPV/r, atazanavir, and tipranavir, complicate appropriate dosing of TDF.

Other Factors and Considerations:

- The fixed-dose combination of TDF and emtricitabine and other available three-drug fixed-dose combination formulations containing TDF allow for once-daily dosing of a single-tablet regimen, which may help improve adherence.
- Both emtricitabine and lamivudine, and TDF have antiviral activity and efficacy against hepatitis B virus (HBV).

Recommendations:

- Based on virologic efficacy and ease of dosing, 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 BMD observed in adults and children receiving TDF and its unknown clinical significance, 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.

Efficacy in Clinical Trials:

- 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.[116]

Adverse Effects:

- Data on the safety of this combination in children are extensive and the combination is generally well tolerated.[129]

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- Major toxicities associated with zidovudine/lamivudine are bone marrow suppression, manifested as macrocytic anemia and neutropenia, and an association with lipoatrophy; minor toxicities include GI toxicity and fatigue.
- Compared to abacavir and TDF, zidovudine is associated with greater mitochondrial toxicity.[130,131]

Other Factors and Considerations:

- Dosing information is available for newborns, including premature infants, because zidovudine has been studied extensively as an HIV prophylaxis regimen.

Recommendations:

- Because of the extensive experience and favorable safety profile, 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.[129]
- 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.[101,109]

Didanosine in Combination with Lamivudine or Emtricitabine (BI*)

- The combination of didanosine and emtricitabine allows for once-daily dosing.[32]
- 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 (page 1 of 2)

An ART regimen in treatment-naive children generally contains one NNRTI or one PI boosted with ritonavir or one INSTI **plus** a two-NRTI backbone. 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	
Children aged ≥14 Days to <3 Years[a]	Two NRTIs **plus** LPV/r
Children Aged ≥2 Years to <3 Years	Two NRTIs plus LPV/r
	Two NRTIs plus RAL[b]

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Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children (page 2 of 2)

Preferred Regimens, continued	
Children Aged ≥3 Years to <12 Years	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** twice daily DRV/r
	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** LPV/r
	Two NRTIs **plus** RAL[b]
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** DTG[d]
	Two NRTIs **plus** once daily DRV/r[e]
	Two NRTIs **plus** EVG/c[f]
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents
Alternative Regimens	
Children Aged >14 Days to <3 Years	Two NRTIs **plus** NVP[g]
Children Aged ≥4 Weeks and <2 Years and Weighing ≥3 kg	Two NRTIs **plus** RAL[b]
Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg	Two NRTIs **plus** ATV/r
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** RAL[b]
	Two NRTIs **plus** RPV[h]
Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children, Birth to 3 Months	ZDV **plus** (3TC **or** FTC)
Children Aged ≥3 Months and <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** (3TC **or** FTC)
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children Aged ≥2 Weeks	ddI **plus** (3TC **or** FTC)
	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	TDF **plus** (3TC **or** FTC)

[a] 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.

[b] 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.

[c] 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. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

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[d] DTG is recommended only for those adolescents aged ≥12 years and weighing ≥40 kg.

[e] DRV once daily should not be used in children aged <12 years and if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

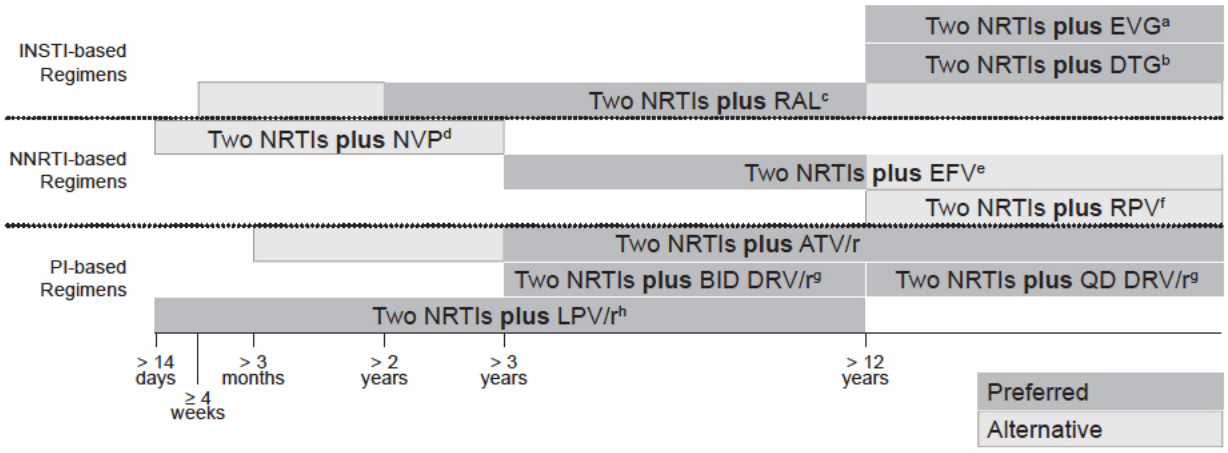
[f] EVG is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir/cobicistat/emtricitabine/TAF are recommended as Preferred for children aged ≥12 years and weighing ≥35 kg. Tablets containing elvitegravir/cobicistat/emtricitabine/TDF are recommended only for adolescents aged ≥12 years, 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] 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; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; 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; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Figure 1. Preferred and Alternative Regimens by Age and Drug Class



[a] EVG is currently recommended only in fixed-dose combination tablets containing elvitegravir/cobicistat/emtricitabine/TAF as Preferred for children aged ≥12 years.

[b] DTG is recommended only for children and adolescents aged ≥12 years and weighing ≥40 kg.

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Use of granules or chewable tablets in infants and children aged 4 weeks to 2 years can be considered as alternative treatment.

[d] 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.

[e] EFV is licensed for use in children aged ≥3 months and weighing ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[f] RPV should only be used if HIV viral load is ≤100,000 copies/mL.

[g] DRV once daily should not be used in children aged <12 years and if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. Depending on weight, a combination of different strength DRV tablets to achieve the targeted dose may be required.

[h] LPV/r should not be administered to neonates before a post-menstrual age (i.e., 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.

Key to Acronyms: ATV = atazanavir; COBI=cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RAL = raltegravir; RPV=rilpivirine; RTV = ritonavir; TAF=tenofovir alafenamide

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Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 1 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order		Integrase Inhibitor Class Advantages: • Susceptibility of HIV to a new class of ARVs • Few drug-drug interactions • Well tolerated	Integrase Inhibitor Class Disadvantages: • Limited data on pediatric dosing or safety
	DTG	• Once-daily administration • Can give with food	• Drug interactions with EFV, FPV/r, TPV/r, and rifampin necessitating twice-daily dosing
	EVG	• Once-daily administration • Available as a tablet and 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) • TAF inhibits tubular secretion of creatinine and may result in increased serum creatinine but with normal glomerular clearance
	RAL	• Can give with food • Available in tablet, chewable tablet and powder formulations	• Potential for rare systemic allergic reaction or hepatitis
NNRTIs In Alphabetical Order		NNRTI Class Advantages: • Long half-life • Less dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens	NNRTI Class Disadvantages: • Single mutation can confer resistance, with cross-resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	• Once-daily administration • Potent ARV activity • Can give with food (but avoid high-fat meals) • Capsules can be opened and added to food	• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • Limited data on dosing for children aged <3 year • No data on dosing for children aged <3 months • Use with caution in adolescent females of childbearing age
	NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food • Extended-release formulation is available that allows for once-daily dosing in older children	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Twice dosing necessary in children with BSA <0.58 m^2
	RPV	• Once-daily dosing • Available in a one-pill daily fixed drug combination	• Should not use in patients with HIV viral load >100,000 copies/mL • Low barrier for resistance

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Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 2 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order		PI Class Advantages: • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well documented • Resistance to PIs requires multiple mutations • When combined with dual NRTI backbone, targets HIV at two steps of viral replication (viral reverse transcriptase and protease enzymes)	PI Class Disadvantages: • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen • Most PIs require ritonavir boosting resulting in associated drug interactions
	ATV/r	• Once-daily dosing • Powder formulation available • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia is common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • RTV component associated with large number of drug interactions
	DRV/r	• Can be used once daily in children aged ≥12 years • Liquid formulation available	• Pediatric pill burden high with current tablet dose formulations • Food effect (should be given with food) • Must be given with RTV boosting to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown • RTV component associated with large number of drug interactions • 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 • 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 • Food effect (liquid formulation should be administered with food) • RTV component associated with large number of drug interactions • 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 • Must be used with caution in patients with preexisting conduction system defects (can prolong PR and QT interval of ECG)

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients; ABC, 3TC are also coformulated with DTG for use in adults	• 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 • 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) • Limited pediatric experience using delayed-release ddI capsules in younger children • Pancreatitis, lactic acidosis, neurotoxicity with ddI
	TAF **plus** FTC for adolescents ≥12 years	• Once-daily dosing • Less tenofovir-associated renal and bone toxicity with TAF compared to TDF in adults	• Only available as a fixed-dose combination tablet consisting of EVG, COBI, FTC, and TAF
	TDF **plus** (3TC **or** FTC) for adolescents, SMR IV or V	• Once-daily dosing for TDF • Resistance is slow to develop • Less mitochondrial toxicity than other NRTIs • Can give with food • TDF and FTC are co-formulated as single pill for older/larger patients • Available as reduced-strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential bone and renal toxicity, toxicity may be less in postpubertal children • 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 • ZDV and 3TC are coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily	• Bone marrow suppression with ZDV • Lipoatrophy with ZDV
	ZDV **plus** ABC	• Palatable liquid formulations • Can give with food	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment • Bone marrow suppression and lipoatrophy with ZDV
	ZDV **plus** ddI	• Extensive pediatric experience • 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 • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation is less palatable than 3TC or FTC liquid formulation • 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 for more information.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; 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; 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; ZDV = zidovudine

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What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated March 1, 2016; last reviewed March 1, 2016)

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 ARVs, 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 who weigh >39 kg and 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 HIV-Infected Children (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.

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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 three drug classes (e.g., NRTI plus NNRTI plus PI or INST plus NRTI plus PI/NNRTI). Although studies containing three classes of drugs have demonstrated these regimens to be safe and effective in previously treated HIV-infected children and adolescents, these regimens have not been studied as initial therapy in treatment-naive children and adolescents and have the potential for inducing resistance to three drug classes, which could severely limit future treatment options.[17-21] Ongoing studies, however, are investigating three drug classes as treatment in HIV-infected neonates.

Regimens Containing Three NRTIs and an NNRTI

Data are currently insufficient to recommend a regimen of three NRTIs plus an NNRTI in young infants. A recent review of nine cohorts from 13 European countries suggested superior responses to this four-drug regimen when compared to boosted PI or three-drug NRTI regimens.[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 three-drug regimen versus a four-drug regimen (three NRTIs and an 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 improvement and virologic control were observed in the four-drug arm, these benefits were not sustained after de-intensification to the three-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 three-drug regimens and lack of additional efficacy data on the four-drug regimen, the Panel does not currently recommend this regimen.

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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

A number of 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 pharmacokinetic (PK) and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (CCR5 antagonist), 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 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 younger than 3 years at this time (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). Based on the recommended efavirenz dosage for children younger than 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.

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Elvitegravir-Based Regimens

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 HIV-1-infected ART-naive adults. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is FDA-approved for used 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 and 11 had viral loads <50 copies/mL. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 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 has been used infrequently in children. A dose-finding study in treatment-experienced children aged 2 to 18 years is enrolling patients in four age cohorts using both liquid and tablet formulations. Initial dose is based on body surface area and scaled from recommended adult 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 (page 1 of 2)

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 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

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Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children (page 2 of 2)

Regimen or ARV Component	Rationale for Being Not Recommended
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 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 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 Appropriate dose not determined in young infants
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Insufficient data to recommend
Full-dose **RTV** or use of **RTV** as the sole PI	GI intolerance Metabolic toxicity
Regimens containing three NRTIs and an 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 Appropriate dose has yet to be determined.
TPV-based regimens	Increased dose of RTV for boosting 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; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

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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**
One ARV drug alone (monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs • Monotherapy "holding" regimens associated with more rapid CD4 decline compared to non-suppressive ART	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• Not recommended for initial therapy • 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: • **3TC plus FTC**	• Similar resistance profile and no additive benefit	• No exceptions
• **d4T plus ZDV**	• Antagonistic effect on HIV	• No exceptions
EFV for Sexually Active Adolescent Girls of Childbearing Potential When Reliable Contraception Cannot Be Ensured	• Teratogenicity in primates (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy Teratogenicity	• When no other ARV option is available and potential benefits outweigh risks
NVP as Initial Therapy in Adolescent Girls with CD4 Count >250 cells/mm^3 or Adolescent Boys with CD4 Count >400 cells/mm^3	• 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 • 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 March 1, 2016; last reviewed March 1, 2016)

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, because HIV NAT test results now often are available within a few days, HIV-infected infants are being diagnosed as early as the first days of life. In addition, the recent 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 ARV treatment and subsequent treatment interruption.[1,2] This interest 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 infected infants
- The very limited dosing and safety data for ARV drugs in the newborn period
- The potential for toxicity from ARV agents.

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 ritonavir-boosted lopinavir

For all other ARV drugs, PK and safety data are insufficient to allow recommendations for safe doses appropriate for use in HIV infected neonates.

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 HIV-infected individual.[3,4] The weight-based 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.[5] 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. This dosing regimen will be studied in the IMPAACT P1115 clinical trial. 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.[7] 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

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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. 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 ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir 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.[8] 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 dosing immediately following birth.[9,10] 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.[8]

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.[11] 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.[12] 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 prenatal maternal ART, high maternal viral load) are for use of zidovudine and nevirapine dosed according to the NICHD-HPTN 040 regimen.[13,14] 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 HIV-infected individuals.[15] In this study, both two- and three-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 three-drug regimen had significantly more hematologic toxicity and the powder nelfinavir formulation is no longer commercially available.

Despite these data, combination treatment of infants at high risk of HIV infection before diagnostic test results indicating infection are available has been increasing. 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.[16] As discussed above, the data necessary for safe and appropriate neonatal dosing of all components of a three-drug ARV regimen for treatment of HIV infection are not currently available.

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The risks associated with use of a three-drug ART regimen in neonates as well as the potential benefits, including the possibility of prolonged remission in infected neonates, require further study before a general recommendation can be made. The Panel 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 HIV-Infected Adolescents (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- Antiretroviral therapy regimens must be individually tailored to the adolescent **(AIII)**.
- Reproductive health including preconception care and contraceptive methods, and safe sex techniques to prevent HIV transmission should be discussed regularly **(AI)**.
- All adolescents, including those who are considering pregnancy, should be receiving maximally suppressive antiretroviral therapy **(AII)**.
- Providers should be aware of potential interactions between antiretroviral therapy and hormonal contraceptives that could lower contraceptive efficacy **(AII*)**.
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings **(AIII)**.

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

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

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

Background

Most individuals in the United States who acquired HIV infection through perinatal transmission are now adolescents or young adults. Of the estimated 10,541 persons who acquired HIV infection through perinatal transmission in the United States, 2,574 are aged less than 13 years as of December 2012.[1,2] Most have had a long clinical course with an extensive history of treatment with antiretroviral therapy (ART).[3] Many older youth initially received non-suppressive mono- or dual therapy prior to the availability of combination regimens. Challenges in the treatment of perinatally infected adolescents include extensive drug resistance, complex regimens, and the long-term consequences of HIV and ART exposure.

Most post-pubertal HIV-infected children and adolescents 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 should be used for treatment recommendations.[4]

Dosing of Antiretroviral Therapy for HIV-Infected Adolescents

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 with 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. Therefore, adolescents in early puberty (i.e., SMR I–III) should be receive pediatric dosing, whereas those in late puberty (i.e., SMR IV–V) should follow adult dosing guidelines. However, puberty may be delayed in children who were infected with HIV perinatally,[6] and

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continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher per body weight than the usual adult doses. Therapeutic drug monitoring may help guide therapeutic decisions.

Timing and Selection of ART

Recommendations for initial therapy that are pertinent to adolescents whose SMR is between I and III, which include data and optimal dosing recommendations, 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 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.[7,8]

Adherence Concerns in Adolescents

HIV-infected adolescents 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 HIV-infected adolescents, 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.[9,10] For a further discussion of interventions to promote adherence in adolescents, see the HIV-Infected Adolescents section of the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and a review by Agwu and Fairlie.[11]

A particular challage 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 Infections in Adolescents

Sexually transmitted infections (STIs), including human papilloma virus (HPV), should be addressed in all adolescents. In young men who have sex with men, screening for STIs may require 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 STIs, see the most recent Centers for Disease Control and Prevention guidelines[13] and the Adult and Pediatric Opportunistic Infection Guidelines on HPV among HIV-infected adolescents.[14,15] All HIV-infected female adolescents who are sexually active should receive gynecologic care and all adolescents should be immunized with HPV vaccination.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

HIV-infected adolescents 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 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 section entitled Reproductive Options for HIV-Concordant and Serodiscordant Couples.[17]

The possibility of planned and unplanned pregnancy should also be considered when selecting a 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

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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 guidance in selection of ARV drugs during pregnancy.

Contraceptive-Antiretroviral Drug Interactions

HIV-infected women can use all available contraceptive methods, including the transdermal patch and vaginal ring.

Several PI and non-nucleoside reverse transcriptase inhibitor 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 Antiretroviral 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 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.

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.[6]

HIV-Infected Pregnant Adolescents and Outcomes

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 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).[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, timing of initiation of treatment and 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 HIV-infected women, including adolescents, are provided in the Perinatal Guidelines.[17] Pregnancies are currently being reported as perinatally infected girls enter adolescence and young adulthood.[22,23] 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.[23-25] However, the rate of perinatal transmission among perinatally infected pregnant women who are receiving ART appears similar to that among women on ART who were infected by horizontal transmission.[26-30]

Transition of Adolescents into Adult HIV Care Settings

Facilitating a seamless transition of HIV-infected adolescents 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."[31] 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.

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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.[32-35] Currently there is no definitive model of transition to adult HIV care and only limited reports about outcomes following transition. A report from the United Kingdom suggests an increased risk of mortality after transition.[34] In the United States, 19.8% (or 91/647) of participants followed in HIV Research Network sites were lost to follow-up after transitioning to adult clinics at age 21 years.[36]

Some general guidelines are available about transitional plans and who might benefit most from them.[37-44] 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;
- Beginning discussions regarding transition early and before the actual transition process.

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy and again before changing regimens **(AIII)**.
• Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**.
• At least one method of measuring adherence to antiretroviral therapy should be used in addition to monitoring viral load **(AIII)**.
• Once-daily antiretroviral regimens and regimens with low pill burden should be prescribed whenever feasible **(AII*)**.
• To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care **(AII*)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*
† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression.[1-3] Prospective adult and pediatric studies have established a direct correlation between risk of virologic failure and the proportion of missed doses of antiretroviral (ARV) drugs.[4] Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, as well as sub-therapeutic or partial dosing.[5] Poor adherence will result in sub-therapeutic plasma ARV drug concentrations, facilitating development of drug resistance to one or more drugs in a given regimen, and possibly 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.[6] 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 HIV-infected children and adolescents. 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 parents—have been associated with non-adherence. However, no consistent predictors of either good or poor adherence in children have been consistently identified.[7-9] Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.[10] These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with 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.[8] The limited availability of palatable formulations and once-daily regimens for infants and young children is especially problematic.[4] Furthermore, infants and children are dependent on

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others for medication administration; thus, assessment of the capacity for adherence to a complex, multidrug regimen requires evaluation of the caregivers and their environments, as well as the ability and willingness of a child to take the drug. Barriers faced by adult caregivers that can contribute to non-adherence in children include forgetting doses, changes in routine, being too busy, and child refusal.[11,12] Some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks,[13] whereas others themselves face health and adherence challenges related to HIV infection, substance use, or mental health and other medical conditions. Other barriers to adherence include caregivers' unwillingness to disclose HIV infection status to the child and/or others, reluctance of caregivers to fill prescriptions locally, hiding or relabeling of medications to maintain secrecy within the household, absence of social support, and a tendency for doses to be missed if the parent is unavailable. Adherence may also be jeopardized by social issues within a family (e.g., substance abuse, unstable housing, poverty, involvement with the criminal justice system).[14]

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 include nursing, social, and behavioral assessments of factors that may influence adherence by children and their families and can be used to 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 minor adverse effects of ARV drugs (e.g., nausea, headaches, abdominal discomfort) that may recede over time or respond to change in diet or timing of medication administration.

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.[15-17] Viral load monitoring is the most useful indicator of adherence and should be used routinely for all patients 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.[18] Use of at least one other method in addition to monitoring viral load to assess adherence is recommended.[17,19] Other measures include quantitative self report of missed doses by caregivers and children or adolescents (i.e., focusing on missed doses during a recent 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Patients, caregivers, and health care providers often overestimate adherence, but admission of missed doses or suboptimal adherence is highly correlated with poor therapeutic response.[20] Targeted questions about stress, pill burden, and daily routine are recommended. A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports.[21]

Home visits can play an important role in assessing adherence. In some cases, suspected non-adherence is confirmed only when dramatic clinical responses to ART occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma ARV drug concentrations or therapeutic drug monitoring may be useful measures in situations where non-adherence is suspected. Drug concentrations in hair are currently being studied as an alternative method to measure adherence but are primarily useful in research studies, as are[22,23] electronic monitoring devices (e.g., Medication Event Monitoring System [MEMS] caps, Wisepill) that are equipped with a computer chip that records each opening of a medication bottle. Mobile phone-based and adherence device technologies (e.g., interactive voice response, SMS text messaging) are being investigated to quantify missed doses and provide real-time feedback to patients and caregivers, but studies in the pediatric population are in the pilot phase.[24-26]

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Strategies to Improve and Support Adherence

Intensive follow-up is required, particularly during the first few months after therapy is initiated. This is particularly important if treatment must be started urgently. 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.[13,27,28] The evidence is mixed as to the efficacy of programs designed for administration of directly observed therapy (DOT) to improve adherence, but DOT may be a useful strategy for particular patients.[27,29-33] Table 11 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 four evidence-based HIV medication adherence strategies) to HIV care providers (located at http://www.effectiveinterventions.org/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence.aspx).[34]

Regimen-Related Strategies

ARV drug regimens for children often require taking multiple pills or unpalatable liquids, each with potential adverse effects 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 adverse effects (AEs).[35] Efforts should be made to reduce the pill burden and to prescribe a once-daily ARV drug 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, 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.[36-39] When non-adherence 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).[40] 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.[41] Finally, if drug-specific toxicities are thought 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 an HIV-infected 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

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to promote adherence.[42] Availability of mental health services and the treatment of mental health disorders (such as depression) may facilitate adherence to complex ARV drug regimens.[43] 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.[44] 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; using beepers or pagers as an alarm; 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.[45-49] Motivational interviews, including computer-based interventions, are currently being evaluated.[42,50] A study evaluating the efficacy of a four-session, individual, clinic-based, motivational, interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months in youth taking ART. However, reduction in viral load was not maintained at 9 months.[51]

Health Care Provider-Related Strategies

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.[52] 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.[53] 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. Strategies to Improve Adherence to Antiretroviral Medications (page 1 of 2)

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 for 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 1) the relationship between partial adherence and resistance; and 2) 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.
• 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.
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.

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Table 11. Strategies to Improve Adherence to Antiretroviral Medications (page 2 of 2)

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, pagers, 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 March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- In children who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) **(AII*)**.
- When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen **(AI*)**.
- The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity **(AIII)**.
- Dose reduction is not a recommended option for management of ARV toxicity, except for those few ARV drugs (e.g., efavirenz) for which a therapeutic range of plasma concentrations detected by therapeutic drug monitoring correlates with toxicity **(AII*)**.

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

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

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

Medication Toxicity or Intolerance

The goals of antiretroviral therapy (ART) include achieving and maintaining viral suppression and improving immune function, with a regimen that is not only effective but also as tolerable and safe as possible. This requires consideration of the toxicity potential of a ART regimen, as well as the individual child's underlying conditions, concomitant medications, and prior history of drug intolerance or viral resistance.

Adverse effects (AEs) have been reported with use of all antiretroviral (ARV) drugs, and are among the most common reasons for switching or discontinuing therapy, and for medication nonadherence. However, rates of treatment-limiting AEs in ARV-naive patients enrolled in randomized trials or large observational cohorts appear to be declining with increased availability of better-tolerated and less toxic ART regimens and are generally less than 10%.[1-11] In general, the overall benefits of ART outweigh its risks, and the risk of some abnormal laboratory findings (e.g., anemia, renal impairment) may be lower with ART than in its absence during HIV infection.

ARV drug-related AEs can vary in severity from mild to severe and life-threatening. 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 some 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.[12-14] 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).[13-16] For a few other ARV drugs, known 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 AEs (see below and Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection).

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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

Management of medication-related toxicity should take into account its severity, the relative need for viral suppression, and the available ARV options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution. However, even mild AEs may have a negative impact on medication adherence and should be discussed before therapy is initiated, at regular provider visits, and at onset of any AEs. 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.[17-19] 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.[20,21] 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 12l), 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.[22-26] Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is 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).

TDM may be used in the management of a child with mild or moderate toxicity if the toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range[27,28] (see Role of Therapeutic Drug Monitoring). This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then, it should be used with caution; an expert in the management of pediatric HIV infection should be consulted.

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To summarize, management strategies for drug intolerance include:

- Symptomatic treatment of mild-to-moderate transient side effects.
- If necessary, change 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 central nervous system symptoms).
- Change drug class, if necessary (e.g., from a PI to an INSTI or a NNRTI or vice versa) and if a patient's virus is susceptible to a drug in that class.
- Dose reduction only when drug concentrations are determined to be above the therapeutic range.

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Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (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: • 1–6 days after starting LPV/r Presentation *Neonates/Preterm Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) • Non-CNS-associated toxicity may include cardiac toxicity and respiratory complications.	Exact frequency of ethanol and propylene glycol-associated toxicity unknown in neonates receiving LPV/r oral solution.	Prematurity Low birth weight 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. 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: • 1–2 days after initiating treatment • 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. Presentation (May Include One or More of the Following) *Neuropsychiatric Symptoms:* • Abnormal dreams • Psychosis • Suicidal ideation or attempted/completed suicide • Seizures (including absence seizures) or decreased seizure threshold	Variable, depending on age, symptom, assessment method Children: • 24% for any EFV-related CNS manifestations in 1 case series with 18% requiring drug discontinuation • 9% incidence of new-onset seizures reported in 1 study in children aged <36 months, in two of the children the seizures had alternative causes. Adults: • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related severe CNS manifestations including suicidality.	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. Use with caution in the presence of psychiatric illness including depression or suicidal thoughts or with concomitant use of psychoactive drugs. 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). 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.

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Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	EFV, continued	*Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration **Note:** Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.	However, evidence is conflicting about whether EFV use increases the incidence of suicidality.			
	RPV	Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/ nightmare *Other CNS Manifestations:* • Headache • Dizziness • Insomnia	In Adults: • CNS/neuropsychiatric 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. In Children: • 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.	Prior history of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in case of severe symptoms.
	RAL	Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression	Children: • Increased psychomotor activity reported in one child. Adults: • Headache • Insomnia (<5% in adult trials)	Elevated RAL concentrations Co-treatment with TDF or PPI Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.

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Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	DTG	Onset: • 7–30 days after initiating drug Presentation *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation attempt, behavior, or completion *Other CNS Manifestations (Generally Mild):* • Insomnia • Dizziness • Headache	Adults • 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% 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. Discontinuation resulted in resolution of neuropsychiatric symptom in 3 out of 4 patients (in the 4th patient, symptoms resolved slowly despite DTG continuation). For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.
Intracranial Hemorrhage	TPV	Onset: • 7–513 days after starting TPV	Children: • No cases of ICH reported in children. Adults: • 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.
Cerebellar Ataxia	RAL	Onset: • As early as 3 days after starting RAL Presentation: • Tremor • Dysmetria • Ataxia	Two cases reported in adults during post-marketing period.	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration.	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme.	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (e.g., drug-drug interaction) identified and removed.

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 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Dyslipidemia	PIs: • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. NRTIs: • Especially d4T NNRTIs: • EFV > NVP, RPV, and ETR	Onset: • As early as 2 weeks to months after beginning therapy Presentation *PIs:* • ↑LDL-C, TC, and TG *NNRTIs:* • ↑LDL-C, TC, and HDL-C *NRTIs:* • ↑LDL-C, TC, and TG	Reported frequency varies with specific ARV regimen, duration of ART and specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% in young children receiving LPV/RTV 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. In studies of treatment naive adults, 38% and 32% receiving EVG/COBI/FTC/TAF developed abnormal fasting TC and LDL-C (respectively) after 48 weeks compared with 21% and 20% receiving EVG/COBI/FTC/TDF, difference mainly attributable to TAF In 48 adolescents treated with EVG/COBI/FTC/TAF median change from baseline to	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome Fat maldistribution	Prevention: • Low-fat diet • Exercise • Smoking-prevention counseling Monitoring[a] *Adolescents and Adults:* • 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. *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests. *Children with Lipid Abnormalities and/or Additional Risk Factors:* • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:* • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3	Assessment of additional CVD risk factors should be done in all patients. HIV-infected patients are considered to be at moderate risk of CVD.[b] 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 trans fat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician. If receiving d4T, it should be discontinued. If receiving PI-based ART, consider switching to a new PI-sparing ART regimen or PI-based regimen containing boosted ATV or DRV, which are less likely to cause lipid abnormalities. Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails. Some experts suggest treatment in children receiving ARV drugs at cut points recommended by 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] The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL.

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Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated March 1, 2016; last reviewed March 1, 2016) **(page 2 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
			weeks 24 and 36 were 26 mg/dl and 36 mg/dl, respectively for fasting TC, and 10 mg/dl and 17 mg/dl, respectively for direct LDL-C.		months after starting lipid therapy. • 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). • Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.	Initiate Drug Therapy Promptly in Patients with Fasting TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin.[c] Ezetimibe can be considered in addition to statins.[d] Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.[c] Risks must be weighed against potential benefits. Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children. 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

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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 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 12c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (e.g., LPV/r, RTV), but can occur with all ARVs and COBI	Onset: • Early Presentation: • 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. Generally improves with time; monitor for weight loss, ARV adherence.	Reassure patient/caretaker that nausea and vomiting will likely decrease over time. Provide supportive care, including instruction on dietary modification. Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases.
Diarrhea	PIs (particularly NFV, LPV/r, FPV/r), buffered ddI, INSTI (mild)	Onset: • Early Presentation: • Generally soft, more frequent stools	Varies with ARV agent; 10% to 30% in some series	Unknown	Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea. Although data in children on treatment of ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate (should not be used with DTG), bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful. While there are few published data on its use, crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults but **not** in children.
Pancreatitis	ddI, d4T (especially concurrently or with TDF), boosted PIs Reported, albeit rarely, with most ARVs.	Onset: • Any time, usually after months of therapy Presentation: • Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis).	<2% in recent series Frequency was higher in the past with higher dosing of ddI.	Concomitant treatment with other medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced disease Previous episode of pancreatitis	Avoid use of ddI in patients with a history of pancreatitis.	Discontinue offending agent—avoid reintroduction. Manage symptoms of acute episode. 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 12d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia[a]	Principally ZDV	Onset: • Variable, weeks to months Presentation *Most Commonly:* • Asymptomatic or mild fatigue • Pallor • Tachypnea *Rarely:* • Congestive heart failure	HIV-Exposed Newborns: • Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir. HIV-Infected Children on ARVs: • 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV	HIV-Exposed Newborns: • Premature birth • *In utero* exposure to ARVs • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis, particularly with ZDV plus 3TC HIV-Infected Children on ARVs: • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • Malnutrition	HIV-Exposed Newborns: • Obtain CBC at birth. • 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). HIV-Infected Children on ARVs: • Avoid ZDV in children with moderate to severe anemia when alternative agents are available. • Obtain CBC as part of routine care.	HIV-Exposed Newborns: • Rarely require intervention unless Hgb is <7.0 g/dL or anemia is associated with symptoms. • Consider discontinuing ZDV if 4 weeks or more of a 6-week ZDV prophylaxis regimen are already completed (see the Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, malignancies. • For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin if essential to continue ZDV.
Macrocytosis	Principally ZDV; also d4T	Onset: • Within days to weeks of starting therapy • MCV often >100 fL Presentation: • Most often asymptomatic • 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.	None required unless associated with anemia

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Table 12d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia[a]	Principally ZDV	Onset: • Variable Presentation: • Most commonly asymptomatic. Complications appear to be less than with neutropenias associated with cancer chemotherapy.	HIV-Exposed Newborns: • Rare HIV-Infected Children on ARVs: • 2.2% to 26.8% of children on ARVs, depending upon the ARV regimen. 2.2% for ZDV/3TC • Highest rates with ZDV-containing regimens	HIV-Exposed Newborns: • *In utero* exposure to ARVs • Combination ARV prophylaxis, particularly with ZDV plus 3TC HIV-Infected Children on ARVs: • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	HIV-Infected Children on ARVs: • Obtain CBC as part of routine care.	HIV-Exposed Newborns: • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/mm^3, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see the Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen. Consider a trial of G-CSF if essential to continue ZDV.

[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; G-CSF = granulocyte colony-stimulating factor; 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 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated March 1, 2016; last reviewed March 1, 2016) **(page 1 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatic Toxicity Elevated AST, ALT, clinical hepatitis	All ARVs may be associated with hepatitis. NVP and TPV are of particular concern. NVP, EFV, ABC, RAL, and MVC have been associated with hypersensitivity reactions. NRTIs (especially ZDV, ddI, and d4T) are associated with lactic acidosis and hepatic steatosis.	Onset: • Hepatitis generally occurs within the first few months of therapy, but can occur later. • Steatosis presents after months to years of therapy. • HBV-coinfected patients may develop severe hepatic flare with the initiation, withdrawal, or development of resistance to 3TC, FTC, or TDF (especially in patients receiving only one anti-HBV agent). • Hepatitis may also represent IRIS early in therapy, especially in HBV- and HCV-infected patients. Presentation: • Asymptomatic elevation of AST and ALT • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may be component of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis.	Uncommon in children Frequency varies with different agents and drug combinations.	HBV or HCV coinfection Elevated baseline ALT and AST Other hepatotoxic medications (including herbal preparations such as St. John's wort [*Hypericum perforatum*], Chaparral [*Larrea tridentate*], Germander [*Teucrium chamaedrys*]) Alcohol use Underlying liver disease Pregnancy For NVP-Associated Hepatic Events in Adults: • Female with pre-NVP CD4 count >250 cells/mm^3 • Male with pre-NVP CD4 count >400 cells/mm^3 Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.[a] Higher drug concentrations for PIs, particularly TPV.	Prevention: • Avoid concomitant use of hepatotoxic medications. • If hepatic enzymes are elevated >5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP. Monitoring: *For ARVs Other Than NVP:* • 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-coinfected or elevated baseline AST and ALT). *For NVP:* • Obtain AST and ALT at baseline, at 2 and 4 weeks, then every 3 months.	Asymptomatic patients with elevated ALT or AST should be evaluated for other causes and monitored closely (including repeating AST, ALT and checking total bilirubin). If ALT or AST is more than 5–10 times ULN and felt to be possibly or probably associated with ARVs, the potentially offending ARVs should be discontinued. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restarting the offending agent. If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP Hypersensitivity). When clinical hepatitis is associated with lactic acidosis, avoid restarting the most likely agent, including ZDV, d4T, and ddI in particular (see also Lactic Acidosis). Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

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Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated March 1, 2016; last reviewed March 1, 2016) **(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: • First months of therapy Presentation: • Jaundice; otherwise asymptomatic elevation of indirect bilirubin levels with normal AST, and ALT. Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.	HIV-Infected Children Receiving ATV: • In long-term follow-up, 9% had at least 1 total bilirubin level > 5 x ULN and 1.4% experienced jaundice	N/A	Monitoring: • No specific monitoring.	Not necessary to discontinue the offending agent except for cosmetic reasons. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time.
Non-Cirrhotic Portal Hypertension	ddI, d4t	Onset: • Generally after years of therapy Presentation: • GI bleeding, esophageal varices, hypersplenism • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism) • Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis.	Rare: • Probably less than 1%	Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T	Monitoring: • No specific monitoring	Manage complications of GI bleeding and esophageal varices. Discontinue/replace d4T or ddI, if patient is receiving either.

[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 12f. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	Several NRTIs (e.g., d4T, ZDV, ddI) Several PIs (e.g., LPV/r; less often ATV, ATV/r, DRV/r, NFV, TPV/r)	Onset: • Weeks to months after beginning therapy; median of 60 days (adult data). Presentation *Most Commonly:* • Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay *Also Possible:* • Frank DM (i.e., polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	Insulin Resistance *ARV-Treated Adults and Children:* • 6% to 33% Impaired Fasting Glucose *ARV-Treated Adults:* • 3% to 25% *ARV-Treated Children:* • 0% to 7% Impaired Glucose Tolerance *ARV-Treated Adults:* • 16% to 35% *ARV-Treated Children:* • 3% to 4% DM *ARV-Treated Adults:* • 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults) *ARV-Treated Children:* • Rare in HIV-infected children	Risk Factors for Type 2 DM: • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	Prevention: • Lifestyle modification • Although uncertain, avoiding the use of d4T may reduce risk. Monitoring: • Monitor for polydipsia, polyuria, polyphagia, change in body habitus, and acanthosis nigricans. *Obtain RPG Levels at:* • Initiation of ARV therapy • 3–6 months after therapy initiation • Once a year thereafter *For RPG ≥140 mg/dL:* • 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, trans fat, and refined sugars; increased physical activity; cessation of smoking); consider consultation with dietician. Change NRTI (e.g., from d4T, ZDV, or ddI to TDF or ABC). For Either RPG ≥200 mg/dL Plus Symptoms of DM or FPG ≥126 mg/dL: • Patient meets diagnostic criteria for DM; consult endocrinologist. FPG 100–125 mg/dL: • Impaired FPG is suggestive of insulin resistance; consult endocrinologist FPG <100 mg/dL: *Normal FPG, but Does Not Exclude Insulin Resistance:* • 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 75g-OGTT (or if <43 kg, 1.75 g/kg of glucose up to a maximum of 75g); 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; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMI = body mass index; d4T = stavudine; ddI = didanosine; dL = deciliter; DM = diabetes mellitus; DRV/r = ritonavir-boosted darunavir; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = ritonavir-boosted lopinavir; NFV = nelfinavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

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Table 12g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated March 1, 2016; last reviewed March 1, 2016)

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: • 1–20 months after starting therapy (median onset 4 months in 1 case series) Presentation *Usually Insidious Onset of a Combination of Signs and Symptoms:* • Generalized fatigue, weakness, and myalgias • Vague abdominal pain, weight loss, unexplained nausea or vomiting • Dyspnea • Peripheral neuropathy **Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure).	Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L) *Adults:* • 15% to 35% of adults receiving NRTI therapy for longer than 6 months *Children:* • 29% to 32% Symptomatic Severe Hyperlactatemia (>5.0 mmol/L) *Adults:* • 0.2% to 5.7% Symptomatic Lactic Acidosis/Hepatic Steatosis: • 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: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline) • Co-administration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy Preterm Infants: • Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution)	Prevention: • Avoid d4T and ddI individually; co-administration of d4T and ddI is not recommended in an ARV regimen (no exception). • Due to the presence of propylene glycol as a diluent, LPV/r oral solution should never be used in preterm neonates in the immediate postnatal period. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring *Asymptomatic:* • Measurement of serum lactate is not recommended. *Clinical Signs or Symptoms Consistent with Lactic Acidosis:* • 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): • Consider replacing ddI and d4T with other ARVs. • As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. Lactate >5.0 mmol/L (Confirmed with Second Test)[b] or >10.0 mmol/L (Any 1 Test): • Discontinue all ARVs. • Provide supportive therapy (IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). Anecdotal (Unproven) Supportive Therapies: • Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) 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 12h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	See below for specific associations.	Onset: • Trunk and limb fat initially increase within a few months of start of ART; peripheral fat wasting may not appear for 12 to 24 months after ART initiation.	Varies greatly depending upon measure and comparator group Highly Variable in Adults: • Up to 93% Children: • Up to 34%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	See below.	See below Although more typically associated with certain ARVs (e.g., d4T), a regimen review with consideration of changing the regimen should be considered, whenever present
Central Lipohypertrophy or **Lipo-accumulation**	Can occur in the absence of ART, but most associated with PIs and EFV.	Presentation: • 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. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Adults: • Up to 93% Children: • Up to 27%	Obesity before initiation of therapy Sedentary lifestyle	Prevention: • Calorically appropriate low-fat diet and exercise Monitoring: • BMI measurement • Body circumference and waist-hip ratio	Calorically appropriate healthy diet low in saturated fats and simple carbohydrates, and exercise, especially strength training Smoking cessation (if applicable) to decrease future CVD risk Consider switching from PIs and EFV to an INSTI Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Recombinant human growth hormone • Growth hormone-releasing hormone • Metformin • Thiazolidinediones • Anabolic steroids • Liposuction.

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Table 12h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 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: • 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: Up to 59% (particularly in patients on d4T-containing regimens) Children: • Up to 47% (particularly in patients on d4T-containing regimens) • Risk lower (up to 15%) in patients not treated with d4T or ZDV.	Underweight before ART	Prevention: • Avoid use of d4T and ZDV. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Replace d4T (not widely used and recommended only in special circumstances) or ZDV with other NRTIs if possible without loss of virologic control. Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat transplantation • Thiazolidinediones.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; CVD = cardiovascular disease; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; 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*, (http://www.aidsinfo.nih.gov) for a more complete discussion and reference list.

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Table 12i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ Nephrolithiasis	ATV, IDV Although DRV causes crystalluria, it is not associated with increased nephrolithiasis risk.	Onset: • Weeks to months after starting therapy Clinical Findings: • Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	ATV-related nephrolithiasis occurs in <10%.	In adults, elevated urine pH (>5.7) Unknown in children	Prevention: • Maintain adequate hydration. Monitoring: • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV.
Renal Dysfunction	TDF	Onset: • Variable; in adults, weeks to months after initiation of therapy. • Hypophosphatemia appears at a median of 18 months. • Glucosuria may have onset after a year of therapy. Presentation: *More Common:* • Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness. *Less Common:* • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	Adults: • Approximately 2% with increased serum creatinine • Approximately 0.5% with severe renal complications Children: • 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: • Aged >6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • Concurrent use of ddI or PIs (especially LPV/r), and preexisting renal dysfunction • 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. In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also measure serum phosphate. Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time. While unproven, routine monitoring intervals of every 3–6 months might be considered. Abnormal values should be confirmed by repeat testing, and frequency of monitoring can be increased if abnormalities are found and TDF is continued.	If TDF is the likely cause, consider using alternative ARV.

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Table 12i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated March 1, 2016; last reviewed March 1, 2016) **(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: • Within a month of starting treatment Presentation: • Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in GFR.	Common Need to distinguish between true change in GFR 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. 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; GFR = glomerular filtration rate; IDV = indinavir; LPV/r = boosted lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Table 12j. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and Osteoporosis	Any ART regimen Specific Agents of Possible Concern: • TDF • PIs, especially LPV/r	Onset: • Any age; more common in months after initiation of ART. Presentation: • Most commonly asymptomatic; fracture (rare) • Osteoporosis diagnosis in children requires clinical evidence of bone fragility (e.g., fracture with minimal trauma) and cannot rely solely on measured low BMD.	Low BMD: • 7% of a U.S. cohort had a BMD z score less than or equal to –2.0 (87% treated with ART). • 24% to 32% of Thai and Brazilian adolescents had a BMD z score less than or equal to –2.0 (92% to 100% treated with ART).	Longer duration of HIV infection Greater severity of HIV disease Growth delay, pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprog-esterone use Limited weight-bearing exercise	Prevention: • Ensure sufficient calcium and vitamin D intake. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, steroid use). Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Consider obtaining serum 25-OH-vitamin D level.[a] • Obtain DXA.[b]	Ensure sufficient calcium intake and vitamin D sufficiency. Encourage weight-bearing exercise. Reduce modifiable risk factors (e.g., smoking, low BMI, use of steroids, use of medroxyprogesterone). Role of bisphosphonates not established in children Consider change in ARV regimen.

[a] Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth, 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

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Osteopenia and Osteoporosis

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Table 12k. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency[a]	Risk Factors	Prevention/ Monitoring	Management
ARV Toxic Neuropathy[b]	d4T, ddI PIs	Onset: • Variable; weeks to months following NRTI initiation. Presentation: • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia (lowered pain threshold) • Allodynia (non noxious stimuli cause pain) • Decreased or absent ankle reflexes Distribution: • Bilateral soles of feet, ascending to legs and fingertips	HIV-Infected Children: • 1.13% prevalence (baseline 2001); incidence 0.23 per 100 person-years (2001–2006) in a U.S. cohort. • <1% discontinued d4T because of neuropathy in 3 large African cohorts (aged 1 month–18 years; median follow-up 1.8–3.2 years). • 42 out of 174 (24%) in a South African cohort were diagnosed with peripheral neuropathy. 86% were taking d4T, and use of ddI was an additional risk factor. • 4/40 (10%) Indian children taking d4T had abnormal nerve conduction tests. HIV-Infected Adults on d4T: • Prevalence up to 57% • Incidence rates of 6.4–12.1 per 100 person-years	HIV-Infected Adults: • Preexisting neuropathy (e.g., diabetes, alcohol abuse, vitamin B-12 deficiency) • Elevated triglyceride levels • Older age • Poor nutrition • More advanced HIV disease • Concomitant use of other neurotoxic agents (e.g., INH) • Some mitochondrial DNA haplogroups may have increased risk.	Limit use of d4T and ddI. As part of routine care, monitor for symptoms and signs of peripheral neuropathy.	Discontinue offending agent. Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful. Consider referral to a neurologist. Data Are Insufficient to Allow the Panel to Recommend Use of Any of the Following Modalities in Children: • Tricyclic antidepressants • Gabapentin • Pregabalin • Mexiletine • Lamotrigine • 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 12I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (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: • First few days to weeks after starting therapy Presentation: • Most rashes are mild-to-moderate, diffuse maculopapular eruptions. **Note:** Some rashes are the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major).	Common (>10% Adults and/or Children): • NVP, EFV, ETR, FPV, FTC Less Common (5% to 10%): • ABC, DRV, TPV, TDF Unusual (2% to 4%): • LPV/r, RAL, MVC, RPV	• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV). • Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP.	When Starting NVP or Restarting After Interruptions >14 Days: • Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction. • Consider concomitant medications and illnesses that cause rash.	Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement: • Most will resolve without intervention; ARVs can be continued while monitoring.[a] • Antihistamines may provide some relief. Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgias, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., Conjunctivitis): • Manage as SJS/TEN/EM major (see below). Rash in Patients Receiving NVP: • Given elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).
	ENF	Onset: • First few days to weeks after starting therapy Presentation: • Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time.	Adults and Children: • >90%	Unknown	• Routinely assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient. • Ensure patient is injecting as per instructions. • Rotate injection sites.

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Table 12I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (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 frequency column)	Onset: • First few days to weeks after initiating therapy Presentation: • 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 include fever, tachycardia, malaise, myalgia, and arthralgia.	Infrequent: • NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case Reports: • FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL	Adults: • Female gender • Race/ ethnicity (black, Asian, Hispanic)	To Lower the Risk of Reactions to NVP when Starting or Restarting after Interruptions >14 Days: • Utilize once-daily dosing (50% of total daily dose) for 2 weeks, then escalate to target dose with twice-daily dosing, which is associated with fewer rashes.[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used, but use of each is controversial. • Do not reintroduce the offending medication. • 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: • 1–8 weeks Presentation: • Fever • lymphadenopathy • facial swelling • a morbilliform to polymorphous rash • peripheral eosinophilia • atypical circulating lymphocytes • 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 cotrimoxazole. • Role for steroids unclear; suggest consultation with specialist. • Supportive care for end-organ disease • Do not reintroduce the offending medication.
Systemic HSR With or without skin involve-ment and excluding SJS/TEN	ABC	Onset *With First Use:* • Within first 6 weeks *With Re-Introduction:* • Within hours Presentation: • Symptoms include high fever, diffuse	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,	• Screening for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is positive**. The medical record should clearly indicate that ABC is contraindicated. • When starting ABC, counsel patients and families about the signs	• Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness). • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.

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Table 12I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involve-ment and excluding SJS/TEN		skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea). • Symptoms worsen to include hypotension and vascular collapse with continuation. With re-challenge, symptoms can mimic anaphylaxis.		HLA-DQ3. • HSR risk is higher in those of white race compared to those of black or East Asian race.	and symptoms of HSR to ensure prompt reporting of reactions.	
	NVP	Onset: • Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: • 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: • Treatment-naive with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men). • Female gender (risk is 3-fold higher in females compared with males). Children: • 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: • 2-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce risk of reaction.[a] • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • 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. • Avoid NVP use in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in PEP.	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor patient closely. • Do not re-introduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

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Table 12I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (page 4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involve-ment and excluding SJS/TEN	ENF, ETR	Onset: • Any time during therapy. Presentation: • 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. 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. 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. 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; CD4 = CD4 T lymphocyte cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; 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 March 1, 2016; last reviewed March 1, 2016)

In the United States, the majority of HIV-infected children 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 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

- For children who have sustained virologic suppression on their current regimen, changing to a new antiretroviral regimen can be considered in order to facilitate adherence, simplify antiretroviral administration, increase antiretroviral potency, decrease drug-associated toxicities, or improve safety **(BII)**.
- Past episodes of antiretroviral treatment 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. For children who have 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 adverse events, and align their regimens with widely used, efficacious adult regimens.

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. Based on the NEVEREST study, young children (i.e., aged <3 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.[1,2] In the NEVEREST 3 study, young children with history of exposure to nevirapine and with virologic suppression on ritonavir-boosted lopinavir maintained virologic suppression when switched from LPV/r to efavirenz.[3] By extrapolation, replacement of LPV/r with an equally potent protease inhibitor (PI) (e.g., darunavir, atazanavir), raltegravir, or another integrase strand transfer inhibitor 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, zidovudine, or abacavir;

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replacing PIs with non-nucleoside reverse transcriptase inhibitors), including improved lipid profiles, in small cohorts of children.[4-8] 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.[9-11]

Table 13 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 limit activity.[12-16] 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 to 4 weeks after switch to new regimen) is important to ensure that virologic suppression is maintained.

Table 13: 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)	Current Age	Body Size Attained	Potential ARV Regimen Change	Comment[b]
NRTIs				
ABC 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.
	Adolescence	Pubertal maturity (i.e., SMR IV or V)	TDF ABC	Once-daily dosing. Less long-term mitochondrial toxicity. Co-formulation with other ARV drugs can further reduce pill burden.
NNRTIs				
EFV	≥12 years	≥40 kg	ATV/r DRV/r DTG	Smaller pill (DTG), higher barrier to resistance given concern for adherence challenges developing in adolescents.
PIs				
LPV/r Twice Daily[1]	≥1 year	≥3 kg	RAL or ATV/r	Better palatability. Less adverse lipid effect. Lower pill burden. Once-daily dosing (ATV/r).
	≥3 years	N/A	ATV/r EFV DRV/r RAL	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 <3 years.
	≥12 years	≥40 kg	DRV/r ATV/r DTG	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)	Co-formulated: • TDF/FTC/EFV • TDF/FTC/EVG/COBI • TAF/FTC/EVG/COBI • TDF/FTC/RPV • ABC/3TC/DTG	Once-daily dosing. Single pill. Alignment with adult regimens.

[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.

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Table 13: 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)

[c] Because of concerns about long-term adverse effects, d4T may 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; 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 March 1, 2016; last reviewed March 1, 2016)

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 drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen **(AI*)**.
- Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*)**.
- The new regimen should include at least two, but preferably three, fully active antiretroviral medications with assessment of anticipated antiretroviral 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 antiretroviral 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

Definitions of Treatment Failure

Treatment failure can be categorized as virologic failure, immunologic failure, clinical failure, or some combination of the three. Laboratory results must be confirmed with repeat testing before a final assessment of virologic or immunologic treatment failure is made. 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 quantification (LLQ) using the most sensitive assay (LLQ 20–75 copies/mL). Older assays with LLQ of 400 copies/mL are not recommended. Virologic failure is defined for all children as a repeated plasma viral load >200 copies/mL after 6 months of therapy. 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 such infants 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. Among many of those receiving lopinavir/ritonavir (LPV/r), suppression can be achieved without regimen change if efforts are made to improve adherence.[1] However, ongoing non-suppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens—increases the risk of drug resistance.[2] There is controversy regarding the clinical implications of HIV RNA levels between the LLQ and <200 copies/mL in patients on

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antiretroviral therapy (ART). HIV-infected adults with detectable viral loads and a quantified result <200 copies/mL after 6 months of ART generally achieve virologic suppression without regimen change.[3-5] 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.[6,7] 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.[8-10] Repeated or persistent plasma viral load detection above 200 copies/mL (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.[5,10-12]

Immunologic Failure

Immunologic failure is defined as a suboptimal immunologic response to therapy or an immunologic decline while on therapy. While there is no standardized definition, many experts would consider as suboptimal immunologic response to therapy the failure to maintain or achieve a CD4 T lymphocyte (CD4) cell count/percentage that is at least above the age-specific range for severe immunodeficiency. Evaluation of immune response in children is complicated by the normal age-related changes in CD4 cell count discussed previously (see Immunologic Monitoring in Children: General Considerations in Clinical and Laboratory Monitoring). Thus, the normal decline in CD4 values with age needs to be considered when evaluating declines in CD4 parameters. CD4 percentage tends to vary less with age. At about age 5 years, absolute CD4 cell count values in children approach those of adults; consequently, changes in absolute count can be used in children aged ≥5 years.

Clinical Failure

Clinical failure is defined as the occurrence of new opportunistic infections (OIs) and/or other clinical evidence of HIV disease progression during therapy. Clinical failure represents the most urgent and concerning type of treatment failure and should prompt an immediate evaluation. Clinical findings should be viewed in the context of virologic and immunologic response to therapy; in patients with stable virologic and immunologic parameters, development of clinical symptoms may not represent treatment failure. Clinical events occurring in the first several months after ART initiation often do not represent ART failure. For example, the development or worsening of an OI in a patient who recently initiated ART may reflect a degree of persistent immune dysfunction in the context of early recovery or, conversely, be a result of immune reconstitution inflammatory syndrome (IRIS). However, clinical failure may occur many months after CD4 cell counts have normalized.[13] The occurrence of significant clinical disease progression should prompt strong consideration that the current treatment regimen is failing.

Discordance Between Virologic, Immunologic, and Clinical Responses

In general, ART that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of HIV-related illnesses. The converse is also generally true: Ineffective ART that fails to suppress viremia is commonly accompanied by immunologic and clinical failure.[14] However, patients may also present with discordant responses, with failure in one domain (e.g., immunologic failure) but with a good response in the other domains (e.g., virologic and clinical response). It is essential to consider potential alternative causes of discordant responses before concluding that ART failure has truly occurred.

Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.[13] Patients with baseline severe immunosuppression often take more than 1 year to achieve immune recovery (i.e., 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

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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 14).

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.[15-19] In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 92 (9.9%) had CD4 cell counts <200 cells/mm^3 at ART initiation and 348 (37%) had CD4 cell counts <500 cells/mm^3. After 1 year of virologic suppression, only 7 (1% of the cohort) failed to reach a CD4 cell count of at least 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.[13]

Certain ARV agents or combinations may be associated with a blunted CD4 response. For example, treatment with a regimen containing tenofovir disoproxil fumarate (TDF) and didanosine can blunt the CD4 response, especially if the didanosine dose is not reduced;[20] this combination is not recommended. If co-administration is unavoidable, dosing of didanosine should be reduced when co-administered with TDF. In adults, ARV regimens containing zidovudine may also impair rise in CD4 cell count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine.[21] Fortunately, this ARV drug-related, suboptimal CD4 cell count response to therapy does not seem to confer an increased risk of clinical events. It is not clear whether this scenario warrants substitution of zidovudine with another drug.

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.

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 IRIS, which does not represent ART failure and does not generally require discontinuation of ART.[22,23] 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.[24] 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, preexisting organ damage, or another reason.[13] 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.[25-29]

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Table 14: 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

Since almost all ARV management decisions for treatment failure are based on addressing virologic failure, this section on managing treatment failure will address only virologic treatment failure (i.e., repeated plasma viral load >200 copies/mL after 6 months of therapy).

The approach to management and subsequent treatment of virologic treatment failure may differ depending on the etiology of the problem. Although the cause of virologic treatment failure may be multifactorial, it is generally the result of nonadherence. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, pharmacokinetic (PK) explanations of low drug levels or elevated, 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 ARV regimen. Table 15 outlines a comprehensive approach to evaluating causes of virologic treatment failure in children, with particular attention to adherence.

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Table 15. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 1 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Nonadherence	1. Interview child and caretaker. • Take 24-hour or 7-day recall. • Obtain description of: • **Who** gives medications • **When** medications are taken/given • **What** medications are taken/given (names, doses) • **Where** medications are kept/administered • **How** medications make child feel, including ability to swallow meds • Have open-ended discussion of experiences taking/giving medications and barriers/ challenges.	• Identify or reengage family members to support/supervise adherence. • Establish fixed daily times and routines for medication administration. • To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are coformulated under a third or fourth name. • Explore opportunities for facility or home-based DOT.
	2. Review pharmacy records. • Assess timeliness of refills. • Ensure that all ARVs are dispensed.	
	3. Observe medication administration. • Observe dosing/administration in clinic. • Conduct home-based observation by visiting health professional. • Admit to hospital for trial of therapy. • Observe administration/tolerance. • Monitor treatment response.	• Simplify medication regimen, if feasible. • Substitute new agents if single ARV is poorly tolerated. • Consider DOT. • Use tools to simplify administration (e.g., pill boxes, reminders [including alarms, cell phone apps], integrated medication packaging for a.m. or p.m. dosing). • As a last resort, consider gastric tube placement to facilitate adherence.
	4. Conduct psychosocial assessment. • Make a comprehensive, family-focused assessment of factors likely to impact adherence with particular attention to recent changes in: • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child's achievement level • Substance abuse (child, caretaker, family members) • Mental health and behavior • Child/youth and caretaker beliefs about ART • Disclosure status (to child and others) • Peer pressure	• Address competing needs through appropriate social services. • Address and treat concomitant mental illness and behavioral disorders. • Initiate disclosure discussions with family/child. • Consider need for child protective services and alternate care settings when necessary.
Pharmacokinetics and Dosing Issues	1. Recalculate doses for individual medications using weight or BSA. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific ARV drugs (see Role of Therapeutic Drug Monitoring).	• Adjust drug doses. • Discontinue or substitute competing medications. • Reinforce applicable food restrictions.

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Table 15. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 2 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
ARV Drug Resistance	1. Perform resistance testing, as appropriate (see Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines).	• If no resistance to current drugs is detected, focus on improving adherence. • If resistance to current regimen is detected, optimize adherence and evaluate potential for new regimen (see Management of Virologic Treatment Failure).

Key to Acronyms: ARV = antiretroviral; ART = antiretroviral therapy; BSA = body surface area; DOT = directly observed therapy

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, predominant plasma viral strains may quickly revert to wild-type and re-emerge as the predominant viral population, in which case resistance testing may 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.[30,31]

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). When efforts to improve adherence will require several weeks or months, many clinicians may choose to continue the current non-suppressive regimen (see Management Options When Two Fully Active Agents Cannot Be Identified or Administered).[32-34] Treatment with non-suppressive regimens in such situations should be regarded as an acceptable but not ideal interim strategy to prevent immunologic and clinical deterioration while working on adherence.[35] Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ARV drug regimen should be reassessed at every opportunity. Complete treatment interruption for a persistently nonadherent patient should prevent accumulation of additional drug resistance but has been associated with immunologic declines and poor clinical outcomes.[36]

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 two, but preferably three, fully active ARV agents from at least two different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence.[37-41] 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

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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.[42]

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 in the Adult and Adolescent Antiretroviral Guidelines 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 received initial therapy with an NNRTI-based regimen, a change to a PI-based regimen or integrase strand transfer inhibitor (INSTI)-based regimen is generally effective. 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 received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen or an INSTI-based regimen is generally effective. LPV/r-based regimens have also been shown to have durable ARV activity in some PI-experienced children.[43-45]

The availability of newer drugs in existing classes (e.g., the NNRTI etravirine) and other classes of drugs (e.g., INSTI) increases the likelihood of finding three active drugs, even for children with extensive drug resistance (see Table 16). Etravirine in combination with darunavir/ritonavir has been shown to be a safe and effective option for children for whom first-line ART fails.[46,47] Etravirine is approved for use in children aged ≥6 years and darunavir in children aged ≥3 years. Raltegravir, an INSTI, is approved for children aged ≥4 weeks.[48] Elvitegravir (coformulated with other ARV drugs), dolutegravir and rilpivirine are approved for use in adolescents aged ≥12 years. Maraviroc, a CCR5 antagonist, is approved for those aged ≥18 years; dose finding studies are ongoing for children aged ≥2 years. Use of newer agents in novel combinations is becoming more common in aging perinatally infected youth in the United States.[49] 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 TDF.[50-52] 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 one, and ideally two, additional active agents.

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Enfuvirtide has been Food and Drug Administration (FDA)-approved for treatment-experienced children aged ≥6 years but must be administered by subcutaneous injection twice daily.[53,54] 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.[55-57] Multidrug regimens (up to three PIs and/or two NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug-drug interactions.[58] Availability of newer PIs (e.g., darunavir) and new classes of ARV drugs (integrase and CCR5 inhibitors) have lessened the need for use of enfuvirtide, dual-PI regimens, and regimens of four or more drugs.

Studies of nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens in adults with virologic failure and multidrug resistance have demonstrated no clear benefit of including NRTIs in the new regimen,[59,60] 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.[60] 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 two fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability and future use of newer therapeutic agents that may not 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.[61] In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child's body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.[62]

Use of ARV agents that do not have a pediatric indication (i.e., off-label) may be necessary for HIV-infected children with 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.[35] 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

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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 four. Only patients in the lamivudine/emtricitabine arm experienced the primary outcome.[63] 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[36] (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 • 2 NRTIs plus INSTI
2 NRTIs plus PI	• 2 NRTIs plus NNRTI • 2 NRTIs plus INSTI • 2 NRTIs plus different RTV-boosted PI • NRTI(s) plus INSTI plus (NNRTI or different RTV-boosted PI)
3 NRTIs	• 2 NRTIs plus NNRTI • 2 NRTIs plus PI • 2 NRTIs plus INSTI • INSTI plus 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	• 2 NRTIs plus INSTI (plus RTV-boosted PI if additional active drug needed) • NRTI(s) plus RTV-boosted PI plus INSTI (consider adding T20 and/or MVC[b] if additional active drug[s] needed) • NRTI(s) plus RTV-boosted DRV or LPVplus ETR (consider adding one or more of INSTI, MVC,[b] or T20 if additional active drug[s] needed) • >1 NRTI plus 2 RTV-boosted PIs (LPV/r plus ATV) (consider adding an INSTI or T20 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 two, but preferably three, fully active drugs for durable, potent virologic suppression. **Please see individual drug profiles for information about 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.

[b] No current FDA-approved pediatric indication for maraviroc

Key to Acronyms: ATV = atazanavir; DRV = darunavir; ETR = etravirine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; T20 = enfuvirtide

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Considerations About Interruptions in Antiretroviral Therapy (Last updated March 1, 2016, last reviewed March 1, 2016)

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 indicated in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient or guardian request. 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 percentage at 4 years, even in those who restarted therapy.[4,5] The case of an infant who initiated ART soon after birth and had a prolonged period without viremia after unplanned interruption is discussed in the Special Considerations for Neonates section.

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.[6] Current Department of Health and Human Services guidelines for adults recommend against planned long-term structured treatment interruptions in adults (see the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents).

In children, there have been fewer studies of long-term structured treatment interruption. In one study, children with controlled viral load (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.[7] However, new drug-resistance mutations were detected in three 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 T lymphocyte (CD4)-guided re-initiation of ART.[8] On average, CD4 values decreased sharply in the first 10 weeks after structured treatment interruption. However, only 34% (19/56) 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

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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% Confidence Interval 0.7–10.4)].[9]

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 reinitiate treatment based on CD4 cell decline. The CHER study in South Africa assessed outcomes in infants randomized to deferred ART (initiation driven by CDC stage and CD4 status), immediate ART with interruption after 40 weeks, or immediate ART with interruption after 96 weeks.[10,11] While the two arms of 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. The long-term outcomes in children after this interruption remain unknown and it is unclear if the short period of time on ART saved by most children merits the potential risks associated with cessation.

Given the increased availability of medications with less toxicity, the potential benefits of structured treatment interruption may not be justified. Current data do not support use of structured treatment interruption in clinical care of HIV-infected children; additional studies of structured treatment interruption in specific situations for some children may be warranted.

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Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- Routine evaluation of plasma concentrations of antiretroviral drugs is not generally recommended in the management of children with HIV infection
- Targeted therapeutic drug monitoring of antiretroviral drugs in children can be considered in the following scenarios **(BII)**:
  - Use of antiretroviral drugs with limited pharmacokinetic data and/or therapeutic experience in children
  - Significant drug-drug and food-drug interactions;
  - Suboptimal treatment response (e.g. lack of virologic suppression) in medication-adherent patients;
  - Suspected suboptimal absorption, distribution, metabolism, or elimination of the drug; or
  - Suspected concentration-dependent drug-associated toxicity.

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 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. Currently, most TDM target concentrations for ARV drugs focus on reaching a trough or minimum concentration (C_{min}).[1] Population average C_{min} for all 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] (page 1 of 2)

Drug	Concentration (ng/mL)
Established Efficacy Plasma Trough Concentrations	
Atazanavir	150
Fosamprenavir	400[b]
Lopinavir	1,000
Nelfinavir[c]	800

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Table 17. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations[a] (page 2 of 2)

Drug	Concentration (ng/mL)
Established Efficacy Plasma Trough Concentrations	
Efavirenz	1,000
Nevirapine	3,000
Maraviroc	>50[d]
Tipranavir	20,500[d]

[a] Adapted from: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* 2014.

[b] Measurable amprenavir concentration

[c] Measurable active (M8) metabolite

[d] Suggested median plasma trough concentration in treatment-experienced patients with resistant HIV-1 strain only

Several adult and pediatric studies have suggested that TDM can have some utility to guide dosing of ARV drugs.[1-10] 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 variability in drug concentrations, and a lack of commercial laboratories willing to provide real-time quantitation of ARV plasma concentrations.

There are special considerations with dosing of ARV drugs in HIV-infected children 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 including ARV drugs in children (particularly very young children) and adolescents compared to adults.[11-13] Suboptimal exposure to selected ARV agents with recommended dosing has been demonstrated in pediatric patients, especially in young children.[7,14,15]

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 pharmacokinetic (PK) modeling, and may be revised as newer PK data become available.[7] While the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children does not recommend routine TDM for pediatric ARV 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

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Additional practical suggestions on TDM of ARV drugs can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee[16] and pediatric TDM manuscripts.[6,17] 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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Conclusion (Last updated March 5, 2015; last reviewed March 1, 2016

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported, new antiretroviral (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. 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 HIV-infected children. Because of the complexity of caring for HIV-infected children, and the decreasing number of children with perinatally acquired HIV in the United States, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist.

The Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics jointly developed and published guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children; these guidelines are available at http://aidsinfo.nih.gov.[1] Similar guidelines for adults are also available at the same website.[2]

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Appendix A: Pediatric Antiretroviral Drug Information

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)
Didanosine (ddI, Videx)
Emtricitabine (FTC, Emtriva)
Lamivudine (3TC/Epivir)
Stavudine (d4T, Zerit)
Tenofovir Disoproxil Fumarate (TDF, Viread)
Zidovudine (ZDV, AZT, Retrovir)

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Abacavir (ABC, Ziagen) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Pediatric Oral Solution: 20 mg/mL

Tablets: 300 mg (scored)

Fixed-Dose Combination Tablets:

With Lamivudine:

- [Epzicom] Abacavir 600 mg plus lamivudine 300 mg

With Zidovudine and Lamivudine:

- [Trizivir] Abacavir 300 mg plus zidovudine 300 mg plus lamivudine 150 mg

With Lamivudine and Dolutegravir:

- [Triumeq] Abacavir 600 mg plus lamivudine 300 mg plus dolutegravir 50 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 (Weight ≥14 kg)

Scored 300-mg tablet.

Weight (kg)	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 can be fatal. Hypersensitivity reactions 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 hypersensitivity reactions. Occurrence of hypersensitivity reactions 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.

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- 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 (≥25 kg)/Adult Dose:
- 300 mg twice daily or 600 mg once daily.

Trizivir
Adolescent (Weight ≥40 kg)/Adult Dose:
- One tablet twice daily.

Epzicom
Adolescent (≥25 kg)/Adult Dose:
- One tablet once daily.

Triumeq
Adolescent (Weight ≥40 kg)/ 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—**

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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 HIV-infected children as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART).

Efficacy

Abacavir used either twice daily or once daily has demonstrated durable antiviral efficacy in pediatric clinical trials.[1-3] A retrospective analysis of observational data from 2 cohorts of African children aged <16 years suggested lower levels of viral suppression in children receiving first-line abacavir/lamivudine-based ART compared to stavudine/lamivudine-based ART; however, observational data may have multiple confounders and further data collection and analysis are needed before conclusions can be drawn (see What to Start).[4,5]

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.[6]

Exposure-Response Relationship

Plasma area under the drug-concentration-by-time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak.[7,8] 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, so the abacavir plasma AUC is frequently considered as a proxy measurement for intracellular concentrations. However, this relationship is not sufficiently strong that changes in plasma AUC can be assumed to reflect true changes in intracellular active drug.[9] Intracellular CBV-TP concentrations are affected by gender and have been reported to be higher in females than in males.[9-11] This effect of gender and the PIs (see Drug Interactions section below) on abacavir PK further complicates linkage of clinically available plasma abacavir concentrations with more difficult to obtain—but pharmacodynamically more important—intracellular CBV-TP concentrations.

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.[12] 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.[11] When combined with darunavir/ritonavir, abacavir plasma AUC and trough concentrations were decreased by

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27% and 38%, respectively; the CBV-TP AUC and trough concentrations were decreased by 12% and 32%, respectively.[13] 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 formulations.[14] There is no difference in the abacavir plasma C_{max} and AUC for abacavir oral solution compared to tablet formulations.[15] 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 HIV 1-infected pediatric subjects aged 3 months through 12 years was evaluated in three trials (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).[14,16-19] 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.[20]

A pediatric PK model developed based on data from 69 children in the PENTA-13 and -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.[21] 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 nucleoside reverse-transcriptase inhibitors zidovudine, stavudine, or didanosine,[1,2,22] and fewer bone and renal toxicities than tenofovir disoproxil fumarate.[23,24]

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Didanosine (ddI, Videx) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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
- Manufacturer recommends 100 mg/m^2 body surface area every 12 hours in this age range. The Panel members interpret pharmacokinetic (PK) data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 body surface area every 12 hours.

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 Body Weight ≥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

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

- Because food decreases absorption of didanosine, administration of didanosine on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. 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. This interaction is more pronounced for the buffered (solution) formulation of didanosine than for the enteric-coated formulation, which is protected from breakdown by gastric acid by the enteric

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Adolescent/Adult Dose

Body Weight (kg)	Dose (mg)
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

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

- This combination should be avoided if possible because of enhanced didanosine toxicity.
- No data on this combination in children or adolescents aged <18 years, but decrease in didanosine dose is recommended as in adults.

Adult Dose of Didanosine when Combined with TDF

Body Weight (kg)	Dose (mg)
<60 kg (limited data in adults)	200 mg once daily
≥60 kg	250 mg once daily

coating instead of co-formulation with antacids.

- 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 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%
- Dosing of didanosine in patients with renal insufficiency: Decreased dosage should be used 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:* The presence of antacids in didanosine oral solution and tablets for oral suspension has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by timing doses to 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 if possible.
- *Renal elimination:* Drugs that decrease renal function can decrease didanosine clearance.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* The combination of stavudine with didanosine may result in enhanced toxicity. That combination should not generally be used (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

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common with didanosine in combination with stavudine. Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir 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.

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

Didanosine is Food and Drug Administration (FDA)-approved for use in children as part of combination antiretroviral therapy.

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.[1,2] Doses higher than 180 mg/m^2 body surface area twice daily are associated with increased toxicity.[3]

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)

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.[4]

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.[5] 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.[6,7] 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.[8]

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Emtricitabine (FTC, Emtriva) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Pediatric Oral Solution: 10 mg/mL

Capsules: 200 mg

Generic Formulations: None available

Fixed-Dose Combination Tablets:

With Tenofovir Disoproxil Fumarate (TDF):

- [Truvada] 300 mg TDF plus 200 mg emtricitabine

With TDF and Efavirenz:

- [Atripla] 300 mg TDF plus 200 mg emtricitabine plus 600 mg efavirenz

With TDF and Rilpivirine:

- [Complera] 300 mg TDF plus 200 mg emtricitabine plus 25 mg rilpivirine

With TDF and Elvitegravir and Cobicistat:

- [Stribild] 300 mg TDF plus 200 mg emtricitabine plus 150 mg elvitegravir plus 150 mg cobicistat

Dosing Recommendations

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

Oral Solution:

- 3 mg/kg once daily.

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:

- 240 mg (24 mL) once daily.

Capsules:

- 200 mg once daily.

Combination Tablets

Truvada

Adolescent (Weight ≥40 kg) and Adult Dose:

- 1 tablet once daily.

Selected Adverse Events

- Minimal toxicity
- Severe acute exacerbation of hepatitis can occur in hepatitis B virus-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 antiretrovirals 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 hepatitis B virus.

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Atripla

Adolescent (Weight ≥40 kg) and Adult Dose:

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

Complera

Adolescent (Weight ≥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.

Stribild

Adult Dose (Aged ≥18 Years):

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

Metabolism/Elimination

- Limited metabolism: No cytochrome P (CYP) 450 interactions.
- Renal excretion 86%: 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 effects 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.

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, or Stribild because emtricitabine is a component of these formulations.
- *Renal elimination:* Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion). Drugs that decrease renal function could decrease clearance.
- *Use with Stribild:* If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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 HIV/hepatitis B virus (HBV)-coinfected patients who changed from emtricitabine-containing to non-emtricitabine-containing regimens.

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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 commonly used as part of a dual-nucleoside reverse transcriptase inhibitor backbone in combination antiretroviral therapy.

Efficacy and Pharmacokinetics

Pharmacokinetics

A single-dose PK study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children aged 2 to 17 years.[1] 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.

A study in South Africa evaluated the PKs of emtricitabine in 20 HIV-exposed infants aged <3 months, given emtricitabine as 3 mg/kg once daily for two, 4-day courses, separated by an interval of ≥2 weeks.[2] 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* μ g/mL). Over the first 3 months of life, emtricitabine AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (N = 6) receiving a single dose of emtricitabine 3 mg/kg after a single maternal dose of 600 mg during delivery, the AUC exceeded that seen in adults and older children, but the half-life (9.2 hours) was similar.[3] Extensive safety data are lacking in this age range.

Efficacy

Based on the aforementioned dose-finding study,[1] emtricitabine was studied at a dose of 6 mg/kg once daily in combination with other antiretroviral (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. In PACTG P1021,[4] emtricitabine at a dose of 6 mg/kg (maximum 240 mg/day as liquid or 200 mg/day as capsules) in combination with didanosine and efavirenz, all given once daily, was studied in 37 ARV-naive HIV-infected children 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.

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

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Lamivudine (3TC, Epivir) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Pediatric Oral Solution: 10 mg/mL (Epivir), 5 mg/mL (Epivir HBVa)

Tablets: 150 mg (scored) and 300 mg (generic); 100 mg (Epivir HBVa)

Fixed-Dose Combination Tablets:

[Combivir and generic] lamivudine with zidovudine:

- 150 mg lamivudine plus 300 mg zidovudine

[Epzicom] lamivudine with abacavir:

- 300 mg lamivudine plus 600 mg abacavir

[Trizivir] lamivudine with zidovudine and abacavir:

- 150 mg lamivudine plus 300 mg zidovudine plus 300 mg abacavir

[Triumeq] lamivudine with abacavir and dolutegravir

- 300 mg lamivudine plus 600 mg abacavir plus 50 mg dolutegravir

Generic Formulations

Tablets: 100 mg, 150 mg, and 300 mg

Dosing Recommendations

Neonate/Infant Dose (Aged <4 Weeks) for Treatment:

- 2 mg/kg twice daily

Note: Please 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 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.

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of lamivudine in the setting of chronic Hepatitis B virus infection.

Special Instructions

- lamivudine can be given without regard to food.
- Store lamivudine oral solution at room temperature.
- Screen patients for Hepatitis B virus 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.

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Weight-Band Dosing (Weight ≥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)	1 ½ tablets 225 mg
≥25 kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets 300 mg

Adolescent/Adult Dose:
Body Weight <25 kg:

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

Body Weight ≥25 kg:

- 150 mg twice daily or 300 mg once daily

Combivir or Generic
Adolescent (Weight ≥30 kg)/Adult Dose:

- 1 tablet twice daily

Trizivir or Generic
Adolescent (Weight ≥40 kg)/Adult Dose:

- 1 tablet twice daily.

Epzicom
Adolescent (Weight ≥25 kg)/Adult Dose:

- 1 tablet once daily

Triumeq
Adolescent (Weight ≥40 kg)/Adult dose:

- 1 tablet once daily

The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (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.

[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 hepatitis B virus (HBV) infection (in people without HIV coinfection). If Epivir HBV is used in HIV-infected patients, 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 infection.

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.

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- *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 treatment of children aged ≥3 months, and it is a common component of most nucleoside backbone regimens.

Efficacy

Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral (ARV) drugs, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response, and it is commonly used in HIV-infected children as a component of a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone.[2-10] In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.[11]

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.[7] 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.[12] 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.[13] 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.[14]

Pharmacokinetics of Liquid Versus Tablet Preparations

The PK of lamivudine have 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 HIV-1-infected adults 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

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unknown.[15] There are currently no studies supporting an increase in dosing for lamivudine oral solution in children. Care should be taken if considering once-daily dosing with the liquid preparation.

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 $(AUC)_{0-24}$ 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.[16] Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children aged 2 to 13 years in the PENTA-13 trial,[2] and in children aged 3 to 36 months in the PENTA 15 trial.[17] Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC_{0-24} 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_{0-24} 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.[18] All three 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.[19] The patients had advanced HIV infection with a mean CD4 percentage of 9 and median plasma RNA of 5.51 $\log_{10}$/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-enteric-coated 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 year 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.[20,21]

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.[22,23]

Both emtricitabine and lamivudine have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, please see the 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 March 1, 2016; last reviewed March 1, 2016)

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

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 Weight <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
- Peripheral neuropathy
- 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.
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- 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.

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- *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 HIV/hepatitis C virus-coinfected patients 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.

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 children, its use is limited 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 appears safe and 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 cotrimoxazole 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

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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] In Pediatric AIDS Clinical Trials Group (PACTG) 219C, peripheral neuropathy was recognized in 0.9% of children.[17]

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 from the United States, Europe, Tanzania, Uganda, and Thailand.[23-29] Lipodystrophy developed in 27% to 66% of children, with lipoatrophy being the most common form of lipodystrophy. The wide range of reported rates of LS is influenced by lack of consensus about clinical definition, ability of clinical staff to identify fat abnormalities in children, measurements used to diagnose abnormalities, duration of follow-up, and population differences. Evaluation of LS in Tanzanian children found that anthropometric measurements predicted LS in well-nourished children, but generally failed to do so in children with lower weights.[26] 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 lipodystrophy have been observed among Thai children after discontinuation of stavudine in two separate studies.[28,30] Improvement or resolution was reported in 22.9% to 73% of cases.

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine.[31-33] In adults, female gender, higher body mass index (BMI), and lower initial CD4 cell count are risk factors for developing lactic acidosis and hyperlactatemia[1] (for additional information on lactic acidosis see Table 12g in Management of Medication Toxicity or Intolerance).

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.[31,34-36] 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.[37]

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.[38,39] Several studies have compared the efficacy and toxicity of the two doses. The 30-mg dose is associated with similar efficacy but significantly lower incidence of peripheral neuropathy than the 40-mg dose.[40,41] However, the overall incidence of toxicity was considered to be unacceptably high.[41] Lipoatrophy and peripheral neuropathy are more likely to occur with higher doses but the risk of lactic acidosis is associated with female gender and a high BMI.[38] When data from 48,785 adult patients from 23 HIV programs in resource-limited countries were evaluated, factors associated with higher toxicity rates included stavudine 40-mg dose, female gender, older age, advanced clinical stage, and low CD4 counts at the time of initiation of therapy.[42] A recent South African study involving 3,910 adult patients on stavudine confirmed higher rates of drug-related toxicity for peripheral neuropathy (OR 3.12), lipoatrophy (OR 11.8), and hyperlactatemia/lactic acidosis (OR 8.37) in patients receiving the 40-mg dose compared to the 30-mg dose. Patients receiving the higher dose also were more likely to discontinue stavudine use (OR 1.71) during the first year on ART.[43] Continued prospective analysis of this cohort has confirmed that treatment initiation with tenofovir disoproxil fumarate has lowered drug-related adverse effects and that stavudine use is declining in

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South Africa.[44] 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.[45] These early studies were conducted at a time when treatment options were limited and many children had failure to thrive. The authors in this early PK study state that stavudine distributes in total body water and, because total body weight correlates well with lean body mass (or weight), stavudine dosages in obese children should be based on lean body weight.[45]

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.[46,47]

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.[48]

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Tenofovir Alafenamide (TAF, Genvoya) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Fixed-Dose Combination Tablets

[Genvoya] Elvitegravir plus cobicistat plus emtricitabine plus tenofovir alafenamide (TAF):

- Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg

Dosing Recommendations

Combination Tablets

Genvoya (Elvitegravir Plus Cobicistat Plus Emtricitabine Plus TAF):

- Adolescent (aged ≥12 years with body weight ≥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
- In 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) 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.

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 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.

Pharmacology

- TAF undergoes renal excretion.
- Dosing in patients with renal insufficiency: Genvoya is not recommended in patients with estimated creatinine clearance below 30 mL per minute.
- Genvoya should not be used in patients with severe hepatic impairment.

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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.
- *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 plus cobicistat plus emtricitabine plus TAF (EVG/COBI/FTC/TAF). 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).

TAF versus TDF

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

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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 HIV-Infected Adults[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)	1918.0 (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

TAF 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.[13-15] TAF shows similar efficacy in children aged at least 12 years and body weight at least 35 kg.[16]

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.[17]

Formulations

Currently TAF is only available as the co-formulated tablet EVG/COBI/FTC/TAF.[17]

Toxicity

Bone

TAF less frequently causes bone toxicity compared to TDF.[13-15] For example in one study of 1733 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]

Renal

Short-term studies in adolescents age 12 to 17 years[16] and 48-week studies in adults[13-15] 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

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(median % change -3% vs. +20%; $P < 0.0001$) at 48 weeks.[13] 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.[18] Monitoring serum lipids while the patient is taking EVG/COBI/FTC/TAF seems reasonable given these data.

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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] Emtricitabine plus tenofovir disoproxil fumarate (TDF):

- 200 mg emtricitabine plus 300 mg TDF

[Atripla] Emtricitabine plus efavirenz plus TDF:

- 200 mg emtricitabine plus 600 mg efavirenz plus 300 mg TDF

[Complera] Emtricitabine plus rilpivirine plus TDF:

- 200 mg emtricitabine plus 25 mg rilpivirine plus 300 mg TDF (Complera)

[Stribild] Emtricitabine plus elvitegravir plus cobicistat plus TDF:

- 200 mg emtricitabine plus 150 mg elvitegravir plus 150 mg cobicistat plus 300 mg TDF (Stribild)

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

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. For

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TDF Tablet Dosing Table
(Aged ≥2 Years and Weight ≥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 (Aged ≥12 Years and Weight ≥35 kg)[a] and Adult Dose:

- TDF 300 mg once daily

Combination Tablets

Truvada (TDF plus emtricitabine):

- Adolescent (aged ≥12 years and weight ≥35 kg) and adult dose: 1 tablet once daily.

Atripla (TDF plus emtricitabine plus efavirenz):

- Adolescent (aged ≥12 years and weight ≥40 kg) and adult dose: 1 tablet once daily.

Complera (TDF plus emtricitabine plus rilpivirine):

- Adolescent (weight ≥35 kg)/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, re-sistance 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 (TDF plus emtricitabine plus elvitegravir plus cobicistat):

- Adolescent (weight >35 kg and SMR 4 or 5)/ 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.

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 12i) 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).

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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:* 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.[2,3] 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.[4,5] Virologic success is lower in treatment-experienced patients with extensive drug resistance.[6-8]

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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.[9] A modeling study suggests that children and adolescents treated with TDF may have higher intracellular TFV-DP concentrations than adults[10] even though plasma TFV concentrations are lower in children and adolescents because renal clearance of TFV is higher in children than in adults.[1,11,12]

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[13,14] and children.[5,15-17] 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).[11] Discontinuation of TDF results in partial or complete recovery of BMD.[15]

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.[6]

TDF administration disrupts vitamin D metabolism[18] 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.[19] 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;[20] 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 pre-pubertal 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 [TAF]) in children in Tanner Stages 1–3, because children with perinatally acquired HIV are at risk for low peak bone mass.[21,22]

Renal

New onset or worsening of renal impairment has been reported in adults[23] and children[24,25] receiving TDF, with renal toxicity leading to discontinuation of TDF reported in 3.7% (6 of 159) of HIV-1-infected children treated with TDF.[8] While TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.[23,24] Irreversible renal failure is quite rare but has been reported.[26]

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The main target of TDF nephrotoxicity is the renal proximal tubule.[24] Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.[27,28]

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.[29] TDF-associated proteinuria or chronic kidney disease is more common with longer duration of treatment.[30,31] 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.[4]

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.[32,33] 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 March 1, 2016; last reviewed March 1, 2016)

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

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:

With Lamivudine:

- [Combivir, generic—scored] 300 mg zidovudine plus 150 mg lamivudine

With Lamivudine plus Abacavir:

- [Trizivir, generic] 300 mg zidovudine plus 150 mg lamivudine plus 300 mg abacavir

Dosing Recommendations

Recommended Neonatal Dosing for Treatment of HIV Infection[a]	
Gestational Age (weeks)	**Zidovudine Oral Dosing:** • Twice-Daily Dosing **Note:** For infants unable to tolerate oral agents, the IV dose should be 75% of the oral dose while maintaining the same dosing interval.
≥35 weeks	**Birth to Age 4 Weeks:** • 4 mg/kg orally twice daily **Aged >4 Weeks:** • 12 mg/kg orally twice daily
≥30 to <35 weeks	**Birth to Age 2 Weeks:** • 2 mg/kg orally twice daily **Aged 2 Weeks to 6 to 8 Weeks:** • 3 mg/kg orally twice daily **Aged >6 to 8 Weeks:** • 12 mg/kg orally twice daily
<30 weeks	**Birth to Age 4 Weeks:** • 2 mg/kg orally twice daily **Aged 4 Weeks to 8 to 10 Weeks:** • 3 mg/kg orally twice daily **Aged >8 to 10 Weeks:** • 12 mg/kg orally twice daily

[a] For prevention of perinatal transmission see Perinatal Guidelines

Selected Adverse Events

- Bone marrow suppression: macrocytosis with or without anemia, neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Nail pigmentation
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Lipoatrophy
- Myopathy

Special Instructions

- Give zidovudine without regard to food.
- If substantial granulocytopenia or anemia develops in patients receiving zidovudine, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- For infants unable to tolerate oral agents, the intravenous dose for newborns should be reduced by 25% while maintaining the same dosing interval.

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Infant/Child Dose (Age ≥35 Weeks Post-Conception and at Least 4 Weeks Post-Delivery):

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

Note: Weight-based dosing table should be used for infants aged ≥35 weeks post-conception, at least 4 weeks post-delivery with body weight ≥4 kg.

Body Surface Area Dosing:

- Oral: 180–240 mg/m^2 body surface area every 12 hours

Adolescent (Aged ≥18 Years)/Adult Dose:

- 300 mg twice daily

Combivir

Adolescent (Weight ≥30 kg)/Adult Dose:

- 1 tablet twice daily

Trizivir

Adolescent (Weight ≥40 kg)/Adult Dose:

- 1 tablet twice daily

Metabolism/Elimination

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

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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).

Resistance mutations were shown to be present in 29% (5 of 17) of infants born to mothers who received zidovudine during pregnancy.[7]

Pediatric Use

Approval

Zidovudine is frequently included as a component of the NRTI backbone for combination antiretroviral therapy (ART).[8-24] Pediatric experience with zidovudine both for treatment of HIV and for prevention of perinatal transmission is extensive.

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%[25] (see the Perinatal Guidelines for further discussion on the use of zidovudine for the prevention of perinatal transmission of HIV). Although the PACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice-daily oral infant dosing for prophylaxis. Zidovudine 4 mg/kg body weight every 12 hours (prophylactic dose) is now recommended for neonates/infants ≥35 weeks of gestation for prevention of transmission (see the Perinatal Guidelines). HIV-exposed but uninfected infants should be continued on the prophylactic dose for 4 to 6 weeks (see Perinatal Guidelines).

For full-term neonates who are diagnosed with HIV infection before age 4 weeks, the zidovudine dose should be increased at age 4 weeks to the continuation dose (see table above). HIV-exposed but uninfected infants should be continued on the initial prophylactic dose until age 6 weeks (see the Perinatal Guidelines). 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.[26] 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.[27] 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.[9] 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.[20]

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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.[8,9,28]

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.[29]

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)

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Efavirenz (EFV, Sustiva) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Capsules: 50 mg, 200 mg

Tablets: 600 mg

Fixed-Dose Combination Tablets:

With Emtricitabine and Tenofovir Disoproxil Fumarate (TDF):

- [Atripla] Emtricitabine 200 mg plus TDF 300 mg plus efavirenz 600 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 Weight ≥3 kg:

- The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (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 is recommended with an efavirenz concentration measured 2 weeks after initiation; some experts would also measure at age 3 years when making the dose adjustment. For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

Children Aged ≥3 Years and Weight ≥10 kg:

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).

Selected Adverse Events

- Rash
- Central nervous system symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures, suicidality
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Potentially teratogenic
- Lipohypertrophy, although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors

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.

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.

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

- 600 mg once daily

Atripla

- Atripla should not be used in pediatric patients <40 kg where the efavirenz dose would be excessive.

Adult Dose:

- One tablet once daily

- 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, indinavir, ritonavir-boosted lopinavir, or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

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

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concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.

- *Rare:* 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:* There is evidence of human fetal risk based on studies in humans (see Pediatric Use section below; see also Efavirenz in the Perinatal Guidelines).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (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 combination antiretroviral therapy in children aged ≥3 months who weigh at least 3.5 kg.

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.[1-4] 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.[3] Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years.[3,5] Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.[6-10]

Pharmacokinetics and Dosing: Infants and Children Aged <3 Years

Limited pharmacokinetic (PK) data in children aged <3 years or who weigh <13 kg have shown that it is difficult to achieve target trough concentrations in this age group.[3,11] 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.[4] This maturation of oral clearance is postulated to result from an increase in the expression of CYP 2B6 with age.[4] 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.[1] 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.[1] 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 HIV-infected and HIV/tuberculosis-coinfected children aged <3 years, using efavirenz dosed by weight band based on CYP2B6 GG/GT versus TT genotype (see Tables 1a and 1b below), showed HIV RNA <400 copies/mL in 61% by intent to treat analysis at 24 weeks.[3] When used without regard to genotype, doses higher than the FDA-recommended doses resulted in therapeutic efavirenz concentrations in an increased proportion of study participants with GG/GT genotypes but excessive exposure in a high proportion of those with TT genotypes.[3] Therefore, dosing tables have been modified so that infants and young children with TT 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.

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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–4.99 kg	200 mg
5 kg–6.99 kg	300 mg
7 kg–13.99 kg	400 mg
14 kg–16.99 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–6.99 kg	50 mg
7 kg–13.99 kg	100 mg
14 kg–16.99 kg	150 mg
≥17 kg	150 mg

[a] Investigational doses are based on IMPAACT study P1070.[3] 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.[5] 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.[5] 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.

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 (search for

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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

laboratory performing this testing at http://www.ncbi.nlm.nih.gov/gtr/labs). Patients should be classified as extensive CYP 2B6 516 GG and GT genotypes versus slow CYP 2B6 516 TT 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, efavirenz plasma concentrations should be measured 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 to guide dose adjustment.

Pharmacokinetics: Children Aged ≥3 Years and Adolescents

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations >1 mcg/mL in adults.[12] Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA levels ≤400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL).[13] 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 mcg/mL or AUC >51 mcg*h/mL.[14]

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, efavirenz concentrations can be suboptimal.[1,14-18] Therefore, some experts recommend therapeutic drug monitoring (TDM) with efavirenz and possibly 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).[13] A PK study in 20 children aged 10 to 16 years treated with lopinavir/ritonavir 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 was lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together.[19] TDM can be considered when using efavirenz in combinations with potentially complex drug interactions. In addition, TDM may be useful if dose reduction is considered. A randomized placebo-controlled multinational trial of adults compared two, once-daily doses of efavirenz (combined with TDF/emtricitabine): efavirenz 600 mg (standard dose) versus efavirenz 400 mg (reduced dose). At 96 weeks, efavirenz 400 mg was non-inferior to efavirenz 600 mg for rate of viral suppression and was associated with fewer reported CNS side effects.[20,21]

Toxicity: Children versus Adults

The toxicity profile for efavirenz differs for adults and children. One adverse effect (AE) commonly seen in

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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 have been reported in more than 50% of patients. 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. 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.[22] This association, however, was not found in analyses of two large observational cohorts.[23,24] In several studies, the incidence of neuropsychiatric adverse effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations.[12,25-28] In patients with preexisting psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS AEs occurred in 14% of children receiving efavirenz in clinical studies[29] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.[2] CNS adverse effects 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: Potential Risk of Teratogenicity

Prenatal efavirenz exposure has been associated with CNS congenital abnormalities in the offspring of cynomolgus monkeys. As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 (2.8%) live births (first-trimester exposure) and 2 of 69 (2.9%) live births (second/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship has not been established between these events and use of efavirenz, similar defects have been observed in preclinical studies of efavirenz.[30]

A recent updated meta-analysis found no association with the potential for teratogenicity following first-trimester efavirenz exposure. However, because of the low incidence of CNS anomalies in the overall population and relatively small number of exposures in the current literature, continued birth outcomes prospective surveillance is warranted.[31] Although the data on the use of efavirenz in pregnancy are reassuring, many experts remain reluctant to consider use of efavirenz in adolescents who are trying to conceive or who are not using effective birth control, so as to avoid the use of efavirenz during the first trimester (the primary period of fetal organogenesis).[32] Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy. Alternate antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception (if such alternative regimens are acceptable to provider and patient and will not compromise a woman's health). 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.[33]

Therapeutic Drug Monitoring

Note: See Role of Therapeutic Drug Monitoring.

In the setting of potential toxicity, it is reasonable for a clinician to use TDM to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.[34,35] This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even

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then, it should be used with caution. Also, the Panel recommends TDM when dosing efavirenz in children aged 3 months to <3 years due to variable PK properties in this young age group. An efavirenz concentration, preferably a trough, measured 2 weeks after initiation, and consultation with an expert, is recommended for dose adjustment. Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations greater than 1000 ng/mL in adults.[12] In addition, some experts would measure efavirenz concentrations at age 3 years for potential dose adjustment if dosing was initiated at age <3 years using investigational dose recommendations.

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Etravirine (ETR, Intelence, TMC 125) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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 daily

Adult Dose (Antiretroviral-Experienced Patients):

- 200 mg twice daily following a meal

Selected Adverse Events

- Nausea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.
- Diarrhea

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.

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- 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.

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Efficacy in Clinical Trials

The PIANO study (TMC125-C213) was a single-arm, Phase II trial involving 101 ARV treatment-experienced, HIV-1 infected pediatric participants aged 6 to <18 years and weighing ≥16 kg. Participants eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA ≥500 copies/mL and viral susceptibility to etravirine at screening. All patients received etravirine with an investigator-selected, optimized background regimen of a ritonavir-boosted PI plus nucleoside/nucleotide analogue reverse transcriptase inhibitors and optional enfuvirtide and/or raltegravir. 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, with a mean CD4 T lymphocyte cell increase of 156 $x10^6/mm^3$.[2] 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%), which the investigators attributed to less advanced disease, less prior NNRTI experience at baseline, and better adherence among the children. However, the population pharmacokinetic (PK) data from this Phase II trial (101 treatment-experienced children aged 6–17 years) revealed slightly lower etravirine exposures in adolescents (aged 12–17 years) compared with children aged 6 to 11 years and with adults (see below).

The safety, efficacy, and tolerability of etravirine in treatment-experienced patients was also evaluated in a multicenter retrospective study of 23 multidrug-resistant pediatric patients with a median age of 14.2 years (interquartile range 12.5 to 15.8 years).[3] The backbone regimen included at least 2 fully active drugs in 91% of patients. During a median of 48.4 weeks of follow-up, 20 patients (87%) achieved HIV-1 RNA <400 copies/mL and 18 of 23 (78%) achieved HIV-1 RNA <50 copies/mL. No patients showed complete resistance to etravirine after follow up but 3 of the 21 patients who interrupted etravirine treatment because of virological or immunological failure had single resistance mutations at baseline.

The efficacy of etravirine-containing regimens in children who have previously been treated with an NNRTI is unclear. However, in a multicenter retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit, et al.[4] found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥4, which would be predicted to compromise its effectiveness.

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 C_{min} were below preset statistical targets based on prior studies involving adults.[5] 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.[6]

	Mean AUC_{0-12h} (ng*h/mL)	Mean C_{0h} (ng/mL)
Children Aged 6–11 Years (N = 41)	5,684	377
Adolescents Aged 12–17 Years (N = 60)	4,895	325
Adults	5,506	393

Key to Acronyms: AUC_{0-12h} = Area under the curve for 12 hours post-dose; C_{0h} = pre-dose concentration during chronic administration

Etravirine is often combined with darunavir/ritonavir for treatment of HIV-infected adults with prior virologic failure. King et al.[7] examined PK data from 37 pediatric patients receiving this combination, all receiving the maximum 200-mg etravirine dose. For both drugs, the estimated 90% confidence intervals for AUC and C_{min} fell below targeted lower limits defined using data from studies in adults. While this combination has been effective in a small cohort of HIV-infected adolescents,[8] and in 51% of participants in the PIANO study,[6] 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

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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) 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 March 1, 2016; last reviewed March 1, 2016)

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

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 (ER) 400 mg only

Suspension: 10 mg/mL

Dosing Recommendations

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

- 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 for dosing.

Treatment of HIV Infection:

Pediatric Dose: Immediate Release and Suspension Formulations

- <1 month: **Investigational dose** not Food and Drug Administration approved
- 34–37 weeks gestational age (no lead in): 4 mg/kg/dose twice daily for the first week increasing to 6 mg/kg/dose twice daily thereafter
- ≥37 weeks gestational age <1 month: 6 mg/kg/dose twice daily (no lead in) (See Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants)

≥1 Month to <8 years:

- 200 mg/m^2 of BSA/dose twice daily after lead-in dosing. In children aged ≤2 years some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 200 mg twice daily).

≥8 Years:

- 120–150 mg/m^2 BSA/dose twice daily after lead-in dosing (Maximum dose of immediate-release tablets is 200 mg twice daily.)
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m^2 dosage as the child grows, as long as there are no untoward effects.[a]

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

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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)

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.[a]

Adolescent/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.

* **Note:** Nevirapine is 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 once daily, of the extended-release preparation. However, in children aged ≤2 years, some experts initiate nevirapine without a lead-in (see Dosing Considerations: Lead-In Requirement). 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 one 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 of different ethnicities, 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 Ritonavir-Boosted Lopinavir section)**.

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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 three-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 infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission; nevirapine-based antiretroviral therapy (ART) is less likely than lopinavir/ritonavir-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 lopinavir/ritonavir. 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/lopinavir/ritonavir arm, $P = 0.0009$. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the protease inhibitor arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the lopinavir/ritonavir arm, $P = 0.027$.[12] Similar results were reported in a comparison study of nevirapine versus lopinavir/ritonavir 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.[13]

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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 HIV-1 infected pediatric participants 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 am 11-day 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.[14] 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.[15]

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 as long as 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 reevaluation 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.[16] The CHAPAS-1 Trial[17] 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 subtherapeutic nevirapine levels

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(<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.[18] 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,[19] 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. This will be studied in the IMPAACT 1115 protocol. 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. PK of nevirapine using the investigational dose will be evaluated as part of IMPAACT 1115. 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 March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Tablet: 25 mg

Fixed-Dose Combination Tablet:

With emtricitabine and tenofovir disoproxil fumarate (TDF):

- [Complera] Rilpivirine 25 mg plus emtricitabine 200 mg plus TDF 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Children Aged <12 Years:

- Not approved for use in children aged <12 years.

Adolescent (Weighing ≥35 kg)/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 (TDF with Emtricitabine plus Rilpivirine):

- Adolescent (Weighing ≥35 kg)/Adult dose: 1 tablet once daily in treatment-naive patients with baseline viral load <100,000 copies/mL or virologically suppressed adults with no history of virologic failure or resistance to rilpivirine and other ARV drugs and currently on their first or second regimen.

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS])
- Hepatotoxicity

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 with mild or moderate hepatic impairment.

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- 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.

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

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

Rilpivirine is approved in combination with other antiretroviral (ARV) agents for treatment-naive, HIV-infected adolescents aged ≥12 years, weighing at least 35 kg, and with viral load ≤100,000 copies/mL. In addition, the combination tablet rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera) is

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approved in virologically suppressed adults (HIV RNA <50 copies/mL) on their first or second regimen with no history of virologic failure or current or past history of resistance to any of the components of Complera.

Pharmacokinetics and Efficacy

The pharmacokinetics (PK), safety, and efficacy of rilpivirine in children aged <12 years have not been established. An international (India, Thailand, Uganda, and South Africa) Phase II trial, Pediatric Study in Adolescents Investigating a New NNRTI TMC278 (PAINT) is investigating a 25-mg dose of rilpivirine in combination with 2 nucleoside reverse transcriptase inhibitors in ARV-naive adolescents aged 12 to <18 years who weigh ≥32 kg and have a viral load ≤100,000 copies/mL.[1]

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.[2]

Rilpivirine Pharmacokinetics in Adolescents and Adolescent/Adult Ratio: PAINT Study[2]

PK Parameter, Geometric Mean (Range)	Adolescent PK	Adolescent/Adult Ratio (95% CI)
Time to Reach Maximum Concentration, Median (range in hours)	5 (2–9)	N/A
C_{max} (ng/mL)	102 (49–182)	0.88 (0.68–1.14)
C_{min} (ng/mL)	51 (20–115)[a]	N/A
C_{0h} (ng/mL)	71 (20–191)	1.21 (0.91–1.61)
C_{24h} (ng/mL)	64 (33–162)	1.10 (0.85–1.41)
AUC_{24h} (ngxh/mL)	1750 (887–3573)	0.98 (0.78–1.25)

[a] Correction provided by personal communication via email from Herta Crauwels, November 11, 2014.

Key to Acronyms: AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; PK = pharmacokinetic

In a PK study of youth aged 13 to 23 years receiving rilpivirine,[3] 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 = 6740 ngxh/mL). No dose adjustments are currently recommended for adults when rilpivirine is used in combination DRV/r , where a similar 2- to 3-fold increase in rilpivirine exposure has been reported.[4]

In the efficacy analysis of the PAINT Study most participants (75%, 28/36) had a baseline viral load ≤100,000 copies/mL. Twenty-two of those 28 (79%) achieved a viral load <50 copies/mL at week 48, while only 50% (4/8) with a baseline viral load >100,000 copies/mL achieved a viral load <50 copies/mL at week 48.[5]

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).[4]

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.

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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)

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Atazanavir (ATV, Reyataz) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Powder Packet: 50 mg/packet

Capsules: 150 mg, 200 mg, and 300 mg

Fixed-Dose Combination Tablets

[Evotaz] Atazanavir with Cobicistat:

- 300 mg atazanavir plus 150 mg cobicistat

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 younger than 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
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- 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.

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Children (≥6 to <18 Years; Weight ≥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 (Aged ≥18 to 21 Years)/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]
  - Administer ritonavir immediately following powder administration.
  - Administer the entire dosage of oral powder within 1 hour of preparation.
- Because atazanavir can prolong the ECG PR interval, use atazanavir with caution in patients with preexisting 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 for recommendations on dosing atazanavir when the drug is co-administered with H2 receptor antagonists). 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

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- 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 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. Under investigation for children and youth aged 12 to 18 years.
- Only boosted atazanavir should be used in combination with TDF because TDF decreases atazanavir exposure.

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 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

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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 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. 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.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors (PPIs) in adults are as follows:

- *Antacids:* Atazanavir concentrations are decreased when the drug is co-administered with antacids and buffered medications (including buffered didanosine formulations); therefore, atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H2-receptor antagonists (unboosted atazanavir in treatment-naive patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV agent. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2 receptor antagonist (a single dose of an H2 receptor antagonist should not exceed a dose comparable to famotidine 20 mg; a total daily dose should not exceed a dose comparable to famotidine 40 mg).
- *H2-receptor antagonists (boosted atazanavir in treatment-naive or treatment-experienced patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV. Dose recommendations for H2 receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily for treatment-naive patients or a ≤20-mg dose equivalent of famotidine twice daily for treatment-experienced patients. Boosted atazanavir (atazanavir 300 mg plus ritonavir 100 mg) should be administered simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist.
- *H2-receptor antagonists (boosted atazanavir with TDF):* Treatment-experienced patients using both TDF and H2-receptor antagonists should be given an increased dose of atazanavir (atazanavir 400 mg plus ritonavir 100 mg plus TDF 300 mg).
- *PPIs:* Co-administration of PPIs with atazanavir is expected to substantially decrease atazanavir plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naive patients are ≤20-mg dose equivalent of omeprazole taken approximately 12 hours before boosted atazanavir (atazanavir 300 mg plus ritonavir 100 mg). Co-administration of atazanavir with PPIs is not recommended in treatment experienced patients.

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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 weight ≥5 kg), children, and adolescents.

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.[2] Unboosted atazanavir at this dose was well tolerated in those aged <13 years who were able to swallow capsules.[3] 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.[2] In this study, the areas under the curve (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 (TDM) is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.[4] Higher target trough concentrations may be required in PI-experienced patients.

Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A[2]

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.

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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 three adult studies and one 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 (≥40kg)[5]

The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.[5] 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).[5] 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.[2]

Assessment of the PK, safety, tolerability, and virologic response of atazanavir oral powder for FDA approval was based on data from two open-label, multicenter clinical trials:

- PRINCE I: In pediatric patients aged 3 months to <6 years[6]
- PRINCE II: In pediatric patients aged 3 months to <11 years[7]

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. Using a modified intent to treat analysis, overall proportions of ARV-naive and ARV-experienced patients with HIV RNA <50 copies/mL at Week 48 were 54% (28/452 and 50% (41/82), respectively. The median increase from baseline in absolute CD4 T lymphocyte count (percent) at 48 weeks of therapy was 215 cells/mm^3 (6%) in ARV-naive patients and 133 cells/mm^3 (4%) in ARV-experienced patients. 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:

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Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE I and II)[a] versus Capsules in Young Adults[b] and Adults[a]

Pharmacokinetic Parameters	Prince Trial[a] ATV/r Dose 150/80 (mg) Body Weight (kg) 5 to <10	Prince Trial[a] ATV/r Dose 200/80 (mg) Body Weight (kg) 5 to <10	Prince Trial[a] ATV/r Dose 200/80 (mg) Body Weight (kg) 10 to <15	Prince Trial[a] ATV/r Dose 250/80 (mg) Body Weight (kg) 15 to <25	Prince Trial[a] ATV/r Dose 300/100 (mg) Body Weight (kg) ≥25 to <35	Young Adult Study[b]	Adult Study[a]
AUC ng•h/mL Mean (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 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 Product Information[7]

[b] The young adults were also receiving TDF; see Kiser, Fletcher et al.[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.[3] 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.[7]

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Darunavir (DRV, Prezista) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Oral suspension: 100 mg/mL

Tablets: 75 mg, 150 mg, 400 mg, 600 mg, and 800 mg

Fixed-Dose Combination Tablets

With cobicistat:

- [Prezcobix] 800 mg darunavir plus 150 mg cobicistat

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 concerns related to seizures and death in infant rats due 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)
10 to <11 kg[a]	darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)
11 to <12 kg[a]	darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL[b])
12 to <13 kg[a]	darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL[b])
13 to <14 kg[a]	darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL[b])
14 to <15 kg	darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL[b])
15 to <30 kg	darunavir 375 mg (combination of tablets or 3.8 mL[c]) plus ritonavir 48 mg (0.6 mL[b])
30 to <40 kg	darunavir 450 mg (combination of tablets or 4.6 mL[c]) 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
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- In patients with one or more darunavir-associated mutation(s), 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 area under the curve (AUC) and maximum plasma concentration (C_{max}) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- Darunavir contains a sulfonamide moiety. The potential for cross sensitivity between darunavir and other drugs in the sulfonamide class is unknown. 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 at room temperature (25° C or 77° F).

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[a] 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.

[b] Ritonavir 80 mg/mL oral solution

[c] The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; however, the PK, efficacy, and safety of darunavir/cobicistat is currently under investigation in children aged 12 to 18 years.

Adolescent (Aged ≥12 Years and Weighing ≥30 kg)/Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations)

30 to <40 kg:

- Darunavir 675 mg (combination of tablets) plus ritonavir 100 mg **once daily**

≥40 kg:

- 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[d] 150 mg (tablet) or coformulated as Prezcobix **once daily with food**

[d] See cobicistat section for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg; Treatment-Experienced with at Least One Darunavir Resistance-Associated Mutation):

- Darunavir 450 mg (combination of tablets) plus ritonavir 100 mg both **twice daily with food**

Adolescent (Aged ≥12 Years and Weighing ≥40 kg)/Adult Dose (Treatment-Experienced with at Least One 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.
- Store oral suspension in the original container at room temperature (25° C or 77° F) and shake well before dosing.

Metabolism/Elimination

- Cytochrome (CYP) P450 3A4 inhibitor and substrate.

Dosing in Patients with Hepatic Impairment:

- Darunavir is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering darunavir to such patients. 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). There are no PK data in patients with severe renal impairment or end-stage renal disease.

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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/)

- 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 are 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 rifampin, is contraindicated with ritonavir- or cobicistat-boosted darunavir.
- Because data are lacking on the plasma concentrations, darunavir/cobicistat should not be used in combination with efavirenz, nevirapine, and etravirine, or other HIV-1 protease inhibitors (including fosamprenavir, saquinavir, or tipranavir).
- When darunavir/ritonavir was used twice daily in combination with etravirine in 40 HIV-infected patients aged 11 to 20 years, both darunavir and etravirine exposure were lower than that found in adults.[1]
- When darunavir/ritonavir twice daily was used in combination with tenofovir disoproxil fumarate (TDF) in 13 HIV-infected patients aged 13 to 16 years, both TDF and darunavir exposures were lower than those found in adults treated with the same combination.[2] No dose adjustment is currently 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.
- 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, or those with baseline elevation 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

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

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.[3] In another 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.[4]

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Pharmacokinetics

Pharmacokinetics in Younger Children

Administration of twice-daily darunavir/ritonavir oral suspension in children aged 3 to <6 years and weighing 10 to <20 kg was conducted in 27 children (see above) who experienced failure of their previous ART regimen and had fewer than three darunavir resistance mutations on genotypic testing.[3,4] 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.[3,4]

Pharmacokinetics in Older Children

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.[5] 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 123.276 mcg*h/mL (range 71.850–201.520) and C_{0h} of 3693 ng/mL (range 1842–7191), 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. 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021976s030,202895s007lbl.pdf. Accessed February 3, 2015.

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).

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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).[6] 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.[5,6] 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.

The data on the dosing of cobicistat with darunavir are available in adult patients only.[7] 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.[8]

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 was used.[9] 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 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 aged ≥12 years 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 two 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).[9-11]

Table B. FDA-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg who are Antiretroviral Treatment-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.

Key to Acronyms: DRV = darunavir; RTV = ritonavir

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Once-Daily Administration in Children Aged <12 Years

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.[9,12] The darunavir/ritonavir dosage 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.[9,12] 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.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone[12]

Pharmacokinetic 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; SD = standard deviation

Once-Daily Administration in Adolescents Age ≥12 Years

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 ≥40 kg body weight) demonstrated darunavir exposures similar to those seen in adults treated with once-daily darunavir (see Table D).[10] 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.[11] 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).[13] 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 TDM in a highly treatment-experienced adolescent patient.[14]

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)[10]	12	800/100 mg	86.7	2,141
Aged 14–23 years (mean 19.5)[13]	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. 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021976s030,202895s007lbl.pdf. Accessed February 3, 2015.

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.[11,15]

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Formulations

Palatability

Darunavir oral suspension is better tasting than the ritonavir oral solution needed for PK boosting, which is seen as a greater challenge to palatability. In a Phase II initial approval study, 27 of the 80 participants switched from the ritonavir liquid solution to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills.[5] Switching to the higher dose of ritonavir for the palatability of the boosting drug can be considered if the liquid formulation represents a barrier. No data are available on the use of cobicistat in pediatric patients.

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Fosamprenavir (FPV, Lexiva) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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 Fosamprenavir Plus Ritonavir 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.

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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 pills can be used in patients weighing ≥33 kg.

Adolescent/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

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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 HIV-Infected Children (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.

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Population	Dose	AUC_{0-24} (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_{0-12} (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 February 12, 2014; last reviewed March 1, 2016)

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

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate/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/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
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- 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 (59–86° 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.

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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:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritus, and rash. Nephrolithiasis/urolithiasis with indinavir crystal deposits.
- *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).
- *Pediatric specific:* The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

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.[1]

Dosing

Both unboosted and ritonavir-boosted indinavir have been studied in HIV-infected children. Data in children indicate that 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.[2-5] 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,[6] that indinavir 234 to 250 mg/m^2 body surface area plus low-dose ritonavir twice daily is too low,[7,8] 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.[8-10]

Toxicity

The cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7% to 34.4%).[11] This is likely due to the difficulty in maintaining adequate hydration in children. Finally, a large analysis of more than 2,000 HIV-infected children from PACTG 219

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demonstrated a hazard ratio of 1.7 for risk of renal dysfunction in children receiving combination antiretroviral therapy with indinavir.[12]

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Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding in patients with hemophilia
- 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.

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- 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
- 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 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.

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Instructions for list).

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 (SQV) and Maraviroc (MVC) doses may need modification (see sections on SQV and MVC).

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.

Major Toxicities

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia,[1] possibly more pronounced in girls than boys.[2]
- *Less common (more severe):* Fat maldistribution
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes

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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 bradyarrhthymias and cardiac dysfunction,[4-6] and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression.[6] 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.

Pharmacokinetics

General Considerations

There is some controversy about the dosing of lopinavir/ritonavir in children. 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[7-9] are compared to those in older children[10] and adults[11] in the table below.

Pharmacokinetics of Lopinavir/Ritonavir by Age

	Adults[11]	Children[10]	Children[10]	Infants[a] at 12 Months[9]	Infants 6 weeks–6 months[7]	Infants <6 weeks[8]
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

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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[12] and with clearance slowing by age 2.3 years.[13] 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.[14]

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[8] and infants aged 6 weeks to 6 months.[7] 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.[9] 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,[15] 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.[10] 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.[10,16] In a study of 15 HIV-infected children 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.[17] 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 subtherapeutic lopinavir trough concentrations,[18] perhaps because of the use of a lower efavirenz dose of approximately 11 mg/kg body weight,[18] compared with efavirenz 14 mg/kg body weight in the Bergshoeff trial.[17]

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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 infection 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.[19-22] Compared with the soft-gel formulation of lopinavir/ritonavir, the tablet formulation has lower variability in trough levels[22,23] but the Panel remains concerned about the long-term effectiveness of once-daily lopinavir/ritonavir in children.

Dosing and Its Relation to Efficacy

Lopinavir/ritonavir is effective in treatment-experienced patients with severe immune suppression,[24,25] although patients with greater prior exposure to ARVs may have slower reductions in viral load to undetectable concentrations[25,26] and less robust response in CD4 T lymphocyte (CD4) percentage.[27] 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%.[27]

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.[28-30] 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).[15] 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.[31]

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.[32]

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.[33] 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.[23]

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.[34-37] The poor weight gain associated with

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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 March 1, 2016; last reviewed March 1, 2016)

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

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/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
- Serum transaminase elevations

Special Instructions

- Administer nelfinavir with meal or light snack.
- If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
- Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, 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.

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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 HIV-infected children.[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 pediatric powder formulation, no longer available, was poorly tolerated when mixed with food or formula. 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 HIV-1-infected children. These findings suggest that CYP2C19 genotypes are important determinants of nelfinavir PKs and virologic response in HIV-1-infected children.[10]

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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 March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Capsules: 200 mg

Tablets: 500 mg

Dosing Recommendations

Neonate/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)/Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg, both twice daily.

Cobicistat is not interchangeable with ritonavir to increase systemic exposure of saquinavir. Saquinavir is not recommended for use in combination with cobicistat.

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

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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 preexisting 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://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

Saquinavir is not Food and Drug Administration-approved for use in children or adolescents aged <16 years.

Efficacy

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors in HIV-infected children.[1-6] Saquinavir plus lopinavir/ritonavir (LPV/r) were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications. Because dual PI therapy is no longer recommended in adult or pediatric guidelines, the Panel does not recommend the use of saquinavir in combination with LPV/r.[1,3-9]

Pharmacokinetics

Studies suggest that saquinavir should not be used without boosting by ritonavir. A pharmacokinetic analysis of 5 children aged <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 aged <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/ritonavir in combination with lopinavir was initiated as second-line therapy based on extensive NRTI resistance (saquinavir was dosed at 50 mg/m^2 body surface area and ritonavir-boosted lopinavir 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]

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Toxicity

In a healthy adult volunteer study, ritonavir-boosted saquinavir 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 (AV) 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 March 1, 2016; last reviewed March 1, 2016)

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

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
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

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

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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 antiretrovirals. 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.
- *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.
- *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.

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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 Food and Drug Administration (FDA)-approved for use in children aged ≥2 years 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 burden of taking 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. However, tipranavir is approved for use in children as young as 2 years and is available in a liquid formulation.

Efficacy

FDA approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of TPV/r in HIV-infected children (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. Recently, the 5-year long-term follow-up 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. Moderate or severe laboratory toxicity (primarily increase in gamma glutamyl transpeptidase and creatine phosphokinase) was seen in 11% of children. 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)

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Enfuvirtide (T-20, Fuzeon) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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/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)/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

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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

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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 HIV-infected children 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 March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Tablets: 150 mg and 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children aged <18 years.
- A pediatric clinical trial is under way.

Adult Dose

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including protease inhibitors (except tipranavir/ritonavir [TPV/r]) and elvitegravir/ritonavir	150 mg twice daily
When given with nucleoside reverse transcriptase inhibitors, enfuvirtide, TPV/r, nevirapine, raltegravir, and 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

Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Orthostatic hypotension (especially in patients with severe renal insufficiency)

Special Instructions

- Conduct testing with HIV tropism assay (see Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines) before using maraviroc to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Use maraviroc in patients with only CCR5-tropic virus. 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.

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- Do not use maraviroc in patients with creatinine clearance <30 mL/min who are receiving potent CYP3A4 inhibitors or inducers.
- Dosing of maraviroc in patients with renal impairment: Refer to the manufacturer's prescribing information.

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 somewhat reduced with ingestion of a high-fat meal; however, maraviroc can be given with or without food.
- *Metabolism:* Maraviroc is a CYP3A4 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.

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 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

The pharmacokinetics (PK), safety, and efficacy of maraviroc in patients aged <18 years have not been established. A dose-finding and efficacy study is under way in children aged 2 to 17 years.[1,2] In this trial, maraviroc dose is based upon body surface area and the presence or absence of a potent CYP3A4 inhibitor in the background regimen. Preliminary PK data are encouraging in those on a potent CYP3A4 inhibitor, but low exposures were seen in those not on a potent CYP3A4 inhibitor. Enrollment and follow-up with participants in this trial continues.

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Integrase Inhibitors

Dolutegravir (DTG, Tivicay, GSK1349572)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

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Dolutegravir (DTG, Tivicay) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Tablet: 50 mg

Fixed-Dose Combination Tablet:

[Triumeq] Dolutegravir plus lamivudine plus abacavir

- Dolutegravir 50 mg plus lamivudine 300 mg plus abacavir 600 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants

Children Aged <12 Years:

- Not approved for use in children aged <12 years. A clinical trial in treatment-experienced children aged <12 years is under way with an experimental dose of 50 mg in children weighing at least 40 kg.

Adolescents (Weighing ≥40 kg)/Adult Dose:

Population	Recommended Dose
Treatment-naive or treatment-experienced/integrase strand transfer inhibitor (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, Lamivudine, and Dolutegravir):

- Adolescent (weighing at least 40 kg)/Adult dose: 1 tablet once daily

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
- 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 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

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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 CYP3A 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 two 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 aged ≥12 years, weighing at least 40 kg, and who are treatment-naive or treatment-experienced and INSTI-naive.[1]

Efficacy and Pharmacokinetics

IMPAACT P1093 is an ongoing open-label trial of HIV-infected children with the plan to enroll down to age 4 weeks. FDA approval of dolutegravir down to age 12 years was based on data from 23 treatment-experienced, INSTI-naive adolescents.[2] 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 revealed 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

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tolerability concerns were identified. By week 144, 39% and 30% had achieved HIV RNA concentrations <400 and <50 copies/mL, respectively.[3] All who experienced virologic failure were nonadherent. In addition, children aged ≥6 to <12 years are undergoing PK and longer-term follow up in P1093, using investigational tablets of lower strengths (or the 50-mg tablet if they weigh at least 40 kg). To date, data from 11 participants have demonstrated a favorable safety profile, adequate PK, and virologic efficacy through 24 weeks.[2,4] An oral pediatric granule formulation is also being studied.

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Elvitegravir (EVG, VITEKTA) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Tablet: 85 mg and 150 mg

Fixed-Dose Combination Tablets:

[Stribild] Elvitegravir plus cobicistat plus emtricitabine plus tenofovir disoproxil fumarate (TDF):

- Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg

[Genvoya] Elvitegravir plus cobicistat plus emtricitabine plus tenofovir alafenamide (TAF):

- Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg

Dosing Recommendations

Note: Elvitegravir should only be used with a pharmacokinetic (PK) enhancer (boosting agent) such as ritonavir as part of a boosted protease inhibitor (PI)-containing regimen, or in combination with cobicistat in Stribild or Genvoya.

Pediatric Dose (Body Weight <35 kg):

- No data on appropriate dose of elvitegravir as Vitekta or in Stribild or Genvoya in children with body weight <35 kg.

Adolescent/Adult Dose (Body Weight > 35 kg):

Genvoya (Any Sexual Maturity Rating; Tanner Stage):[a]

- One tablet once daily

Stribild (SMR 4 or 5)[a]*:*

- One tablet once daily
- Elvitegravir (as Vitekta) in combination with an HIV PI co-administered with ritonavir and another antiretroviral (ARV) drug.[b]

Recommended elvitegravir dosage taken once daily with food (all drugs administered orally)

Dosage of EVG	Dosage of Concomitant PI	Dosage of Concomitant Ritonavir
85 mg once daily	Atazanavir 300 mg once daily	100 mg once daily
	Lopinavir 400 mg twice daily	100 mg twice daily
150 mg once daily	Darunavir 600 mg twice daily	100 mg twice daily
	Fosamprenavir 700 mg twice daily	100 mg twice daily
	Tipranavir 500 mg twice daily	200 mg twice 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.
- Do not use elvitegravir with PIs co-administered with cobicistat (not yet studied), or with other elvitegravir-containing drugs

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including Stribild or Genvoya. 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 a PK enhancer (boosting agent) such as ritonavir as part of a boosted PI-containing regimen or in combination with cobicistat (in Stribild or Genvoya). Refer to those sections for further details.
- Stribild should not be initiated in patients with estimated creatinine clearance <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min because dose adjustments required for FTC 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 Association (FDA)-approved for use in 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.

[b] Elvitegravir as Vitekta is not FDA-approved for use in children aged <18 years. The PK profile is similar to that in adults when given with either atazanavir/ritonavir or lopinavir/ritonavir, or darunavir/ritonavir. Vitekta was well tolerated in adolescents, but the use of a multi-pill regimen was associated with poor adherence and a high percentage of virologic failures, leading to the recommendation for use in adolescents only when elvitegravir is part of a coformulated regimen like 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 (ATP)-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

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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 for use 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 elvitegravir nor Stribild is FDA-approved for use in children aged <18 years.[2,3] In November 2015, Genvoya was FDA-approved for use in youth aged ≥12 years and body weight ≥35 kg.[4]

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.[5] 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 atazanavir/ritonavir (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.[5]

Stribild is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive adults aged ≥18 years 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.[3] Trials have shown non-inferiority of Stribild to regimens of emtricitabine combined with TDF plus ATV/r,[6,7] or emtricitabine plus TDF plus efavirenz.[8,9] 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.[10] Adults who experience a confirmed increase in serum creatinine greater than 0.4 mg/dL from

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baseline should be closely monitored for renal toxicity by following creatinine for further increases and urinalysis for evidence of proteinuria or glycosuria.[3] Because TDF is included in Stribild and can be associated with renal toxicity, careful periodic evaluation of renal function is warranted. This nephrotoxicity may be more pronounced in patients with pre-existing renal disease.[3]

Genvoya is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive individuals aged ≥12 years and body weight ≥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 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.[3] Because Genvoya contains tenofovir alafenamide (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.[11]

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.[12] 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] although its use with ATV/r or LPV/r might be considered in patients in whom adherence could be assured.

Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 years

Studies of the adult dosage formulation of Stribild in HIV-infected youth aged ≥12 years with body weight ≥35 kg have demonstrated PK, safety, and efficacy similar to that in adults through 24 weeks of study.[13-16] Studies of the adult dosage formulation of Genvoya in HIV-infected youth aged ≥12 years with body weight ≥35 kg have shown safety comparable to that of adults, 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. Note that 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 body weight ≥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.[17] Pediatric formulations of both elvitegravir[18] and cobicistat[19] are bioequivalent to adult formulations. Studies are ongoing of pediatric formulations in children aged < 6 years and body weight <30 kg.

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Raltegravir (RAL, Isentress) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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

Note: Film-coated tablets, chewable tablets, and oral suspension **are not interchangeable**.

Dosing Recommendations

Neonate Dose:

- Not approved for use in neonates.
- **Note:** Metabolism by uridine diphosphate glucotransferase (UGT1A1) is immature in neonates. Neonatal dose is being studied.

Infant/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.

Children Aged 2 to <12 Years:

- <25 kg: Chewable tablet twice daily (maximum of 300 mg 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.

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 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

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Chewable Tablet Dosing Table

Dosing[a] of Chewable Tablets in Children Aged 2 to <12 Years:

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.

Note: Maximum dose of chewable tablets is 300 mg twice daily.

Adolescent (Aged ≥12 Years)/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.

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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-infection for use in infants and children aged ≥4 weeks and weighing ≥3 kg. Current pediatric FDA approval and dosing recommendations are based upon evaluations in 122 patients aged ≥4 weeks to 18 years enrolled in IMPAACT P1066.[1]

Efficacy and Pharmacokinetics

Raltegravir pharmacokinetics (PK) exhibit considerable intrasubject and intersubject variability.[2,3] Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naive HIV-infected patients 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.[2,3] 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.[2,3]

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.[4,5]

TABLE A: Summary of P1066 Cohorts and Participation[4,5]

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

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TABLE B: Summary of P1066 PK Results by Cohort[4,5]

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: 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, HIV-infected children and adolescents aged 2 to 18 years in combination with an optimized background ART regimen.[6,7] 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_{0-12h}) 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%).[4,6] 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.[4] 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.

In 19 HIV-infected children and adolescents with 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.[8] Additional experience from the French expanded access program in

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treatment-experienced adolescents support the good virologic and immunologic results observed in IMPAACT P1066.[9,10]

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 geometric mean (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 was well tolerated with good efficacy.[5]

Neonates Aged <4 Weeks

There are no 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.[11]

Washout PK of raltegravir in neonates born to HIV-infected pregnant women was studied in P1097.[12] 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 trial to evaluate the safety and PK of raltegravir in HIV-1 exposed neonates at high risk of acquiring HIV-1 infection (ClinicalTrials.gov identifier: NCT01780831). Enrollment is ongoing and preliminary safety and PK results for the initial cohort have been presented. After combining RAL concentration data from this small group of neonates receiving only two raltegravir doses with that from older infants and children receiving daily dosing, a population PK model and simulations were used to facilitate the development of a daily-dosing neonatal raltegravir regimen for evaluation in a second cohort of neonates.[12,13]

Formulations

The PK of raltegravir was compared in HIV-infected adult patients 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.[14] In adult volunteers, the PK of raltegravir 800 mg taken once daily by chewing was compared to two 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.[15] 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.[16] Inter-patient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.[1,17] Because of the differences in the bioavailability of the chewable tablets, film-coated tablets, and oral suspension, the dosing recommendations are different and these products are not interchangeable.

Palatability was evaluated as part of P1066. Both chewable tablets and oral granules for suspension were

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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.[4,5]

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Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

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Cobicistat (COBI, TYBOST) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Tablets: 150 mg

Fixed-Dose Combination Tablets:

[Stribild] Elvitegravir plus cobicistat plus emtricitabine plus tenofovir disoproxil fumarate (TDF):

- Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg

[Genvoya] Elvitegravir plus cobicistat plus emtricitabine plus tenofovir alafenamide (TAF):

- Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg

[Evotaz] Atazanavir plus cobicistat:

- 300 mg atazanavir plus 150 mg cobicistat

[Prezcobix] Darunavir plus cobicistat:

- 800 mg darunavir plus 150 mg cobicistat

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

Not FDA-Approved for Use in Children Aged <12 Years or Body Weight <35 kg:

- Genvoya

Adolescent and Body Weight ≥35 kg

- Cobicistat 150 mg orally once daily as a component of Genvoya

Adult (Aged ≥18 Years) Dosing:

- Cobicistat must be administered as
  - The combination tablet Stribild or Genvoya, in which case it would not be dosed with any other antiretroviral (ARV) drugs; *or*
  - The tablet Tybost co-administered with atazanavir or darunavir at the doses listed in

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 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 12i). 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).

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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

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor
- 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 CYP3A4 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, 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.

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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 co-formulated 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.[3]

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Ritonavir (RTV, Norvir) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Oral Solution (Contains 43% Alcohol by Volume): 80 mg/mL

Capsules: 100 mg

Tablets: 100 mg

Dosing Recommendations

Ritonavir as a Pharmacokinetic (PK) Enhancer[a]:

- Ritonavir is used as a PK enhancer of other protease inhibitors (PIs) and of an integrase inhibitor (elvitegravir) when elvitegravir is included in a boosted, protease-containing regimen. The recommended dose of ritonavir varies and is specific to the drug combination selected. See dosing information for specific PIs and for elvitegravir.

[a] **Note:** 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).
- If ritonavir is prescribed with didanosine, administer the drugs 2 hours apart.
- Refrigerate ritonavir capsules only if the capsules will not be used within 30 days or cannot be stored below 77°F (25°C). Ritonavir tablets are heat stable.
- Do **not** refrigerate ritonavir oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- Ritonavir oral solution has limited shelf life; use within 6 months.
- Patients who have persistent or significant nausea with the capsule may benefit from switching to the tablet. Also, the tablet is

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smaller than the capsule and thus easier to swallow.

- 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.

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor; CYP3A4 and CYP1A2 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.
  - Avoid concomitant use of intranasal or inhaled fluticasone because of reports of adrenal insufficiency.[1] 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.[2,3]

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

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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.[4]

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 capsules (adult dose is six capsules or 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 or, in adults, with the integrase inhibitor elvitegravir when used in combination with another PI. Ritonavir is a CYP3A4 inhibitor and functions as a PK enhancer by slowing the metabolism of elvitegravir and 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). Dosing of ritonavir when used as a PK enhancer of elvitegravir in a boosted PI regimen is available for adults (see elvitegravir section).

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.[4] Potentially life-threatening arrhythmias in premature newborn infants treated with LPV/r have been reported; thus, LPV/r should not be used in this group of patients.[5,6] 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 March 1, 2016)

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

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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

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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

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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

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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

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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.

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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		Deaths[b]	
	No. Patients[d]	Number	Percentage
≤100,000			
≥15%	103	15	(15%)
<15%	24	15	(63%)
>100,000			
≥15%	89	32	(36%)
<15%	36	29	(81%)

[a] Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

[b] Mean follow-up: 5.1 years.

[c] Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

[d] Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. *J Infect Dis.* 1997;175(5):1029–1038.

Figure A. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

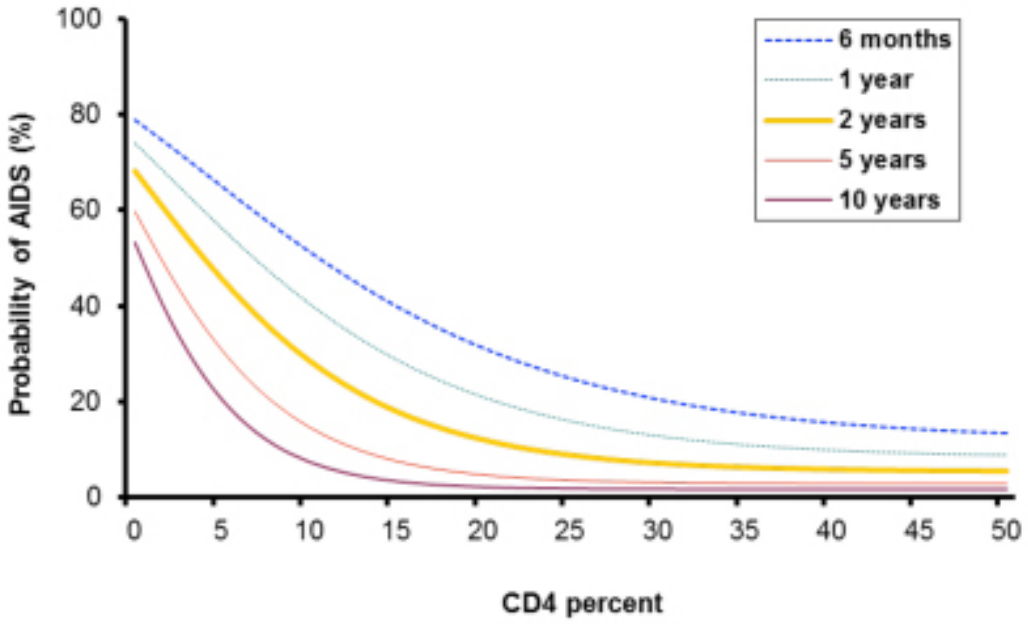

Figure modified from *Lancet* 2003;362:1605-1611

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Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

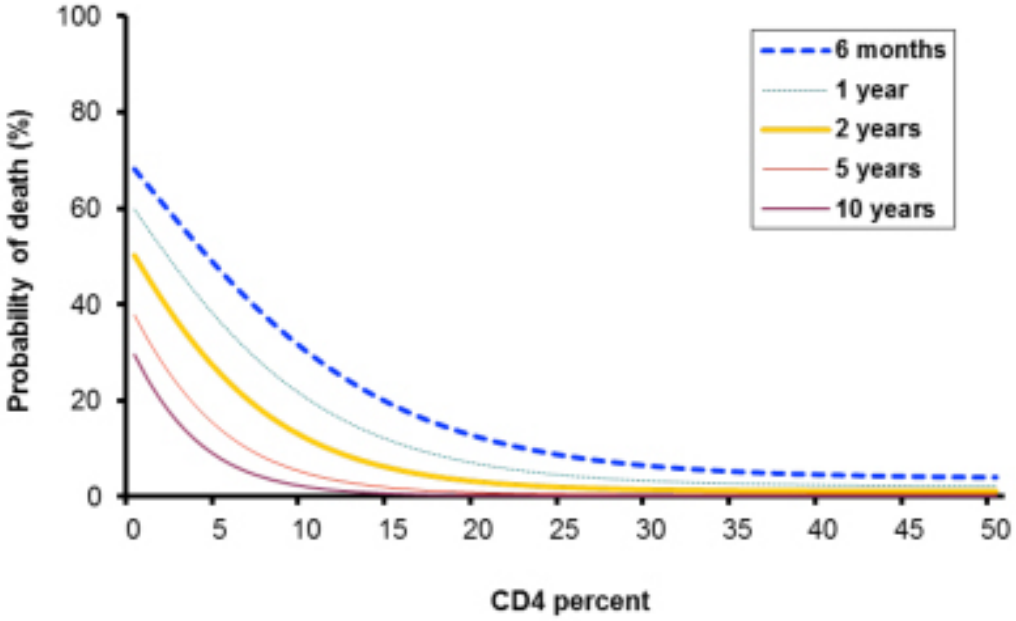

Figure modified from *Lancet* 2003;362:1605-1611

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*

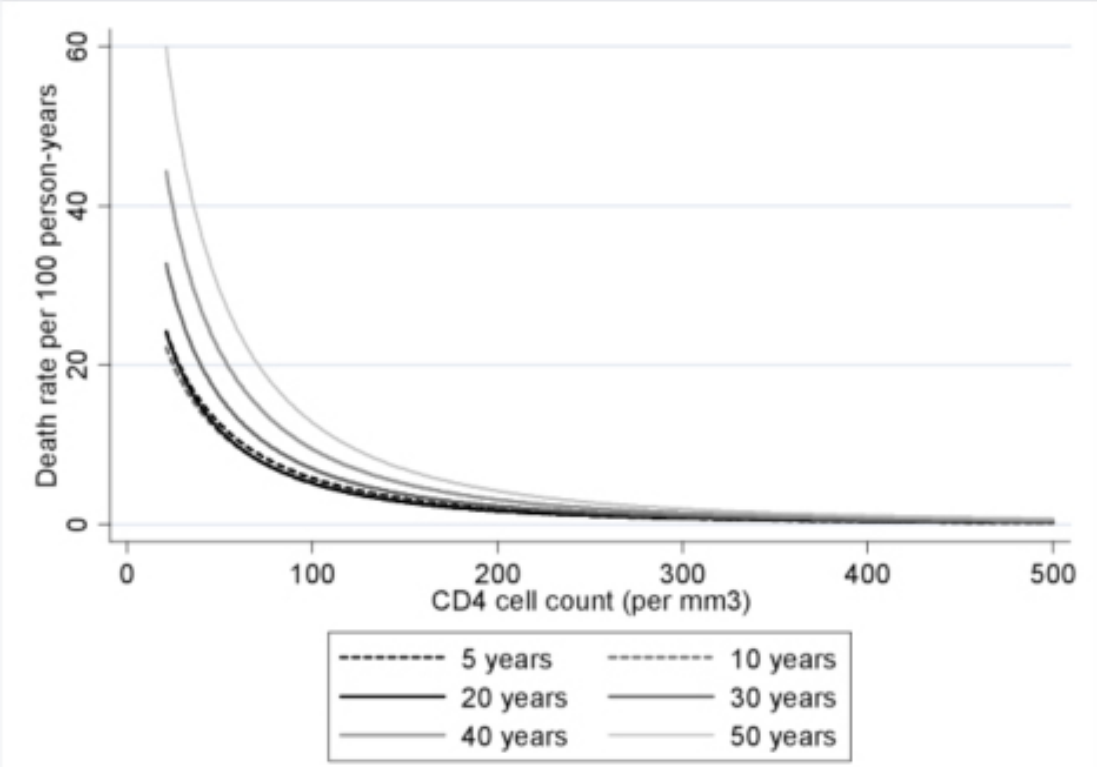

Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis.* 2008;197:398-404.

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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

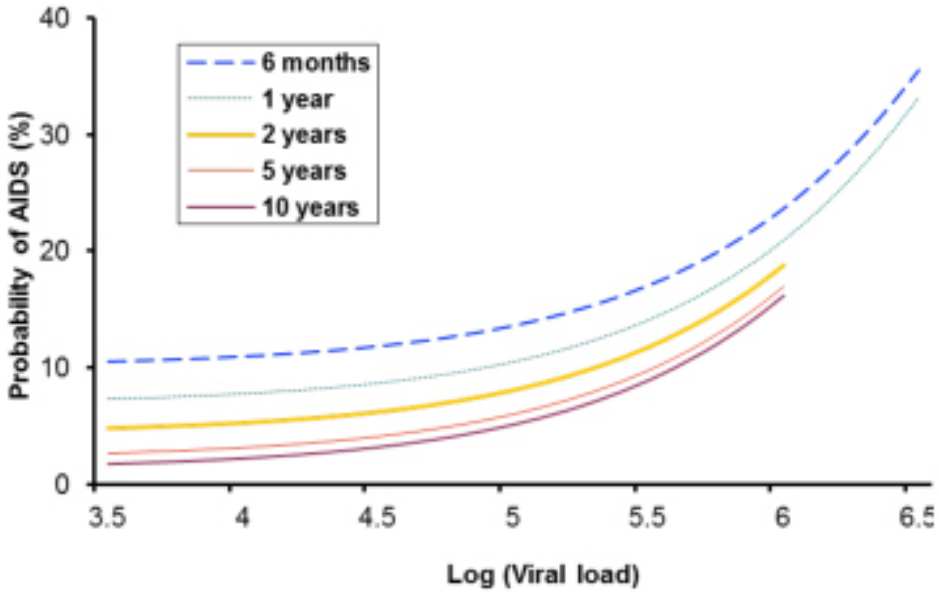

Figure modified from *Lancet* 2003;362:1605-1611

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

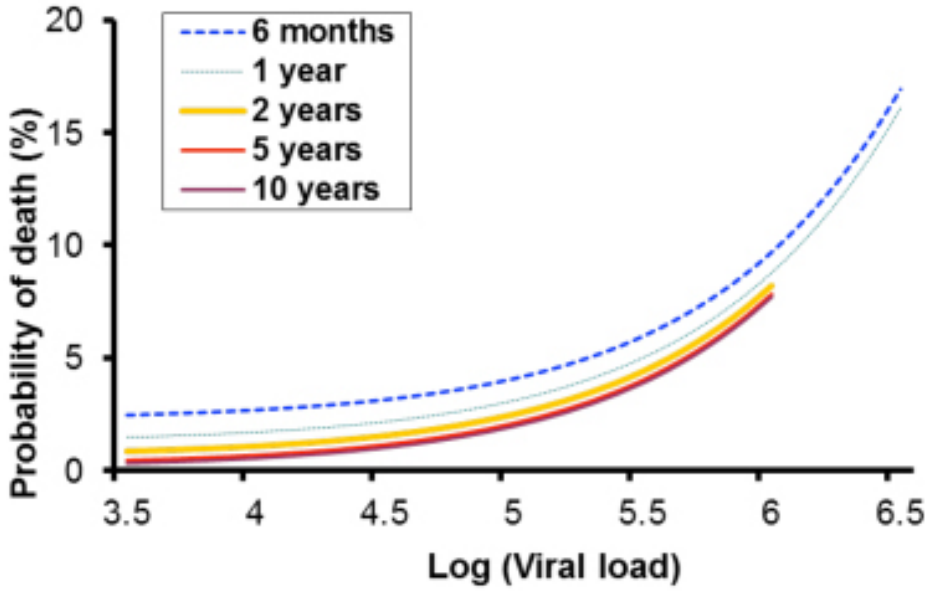

Figure modified from *Lancet* 2003;362:1605-1611

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