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)

How to Cite the Pediatric Guidelines:

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

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What's New in the Pediatric Guidelines (Last updated February 12, 2014; last reviewed February 12, 2014)

Key changes made by the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) to update the November 1, 2012, Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection are summarized below. Some content has been reorganized and condensed to enhance usability. Throughout the document, text and references have been updated to include new publications where relevant. The terms "mother-to-child transmission (MTCT)" and "prevention of mother-to-child transmission (PMTCT)" have been replaced with "perinatal transmission" and "prevention of perinatal transmission," respectively. Minor revisions have been made in toxicity tables and other sections of the document; all changes are highlighted throughout the guidelines. A link to the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children (published November 6, 2013), has been inserted in selected areas of the text to refer readers to more detailed information about use of specific antiretroviral (ARV) agents in the context of hepatitis B, hepatitis C, or tuberculosis coinfection (see the Pediatric Opportunistic Infections Guidelines).

Diagnosis of HIV Infection

- To address the possibility that the sensitivity of diagnostic virologic assays in HIV-exposed infants might be affected by combination ARV prophylaxis, the Panel recommends if the results of prior virologic testing were negative while an infant was receiving prophylaxis, virologic diagnostic testing should be considered 2 to 4 weeks after cessation of ARV prophylaxis for infants receiving combination ARV infant prophylaxis **(BIII)**.

Clinical and Laboratory Monitoring of Pediatric HIV Infection

- Two former sections titled Laboratory Monitoring of Pediatric HIV Infection Prior to Therapy Initiation and Monitoring Children on Antiretroviral Therapy have been combined into a single section with revisions that reflect this modification.
- The Panel now recommends that CD4 T lymphocyte (CD4) cell count/percentage can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy, and who have CD4 levels well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years **(BII)**.
- The Panel has reviewed and updated the schedule for clinical and laboratory monitoring of children before and after initiation of combination antiretroviral therapy (cART) in Table 3.

When to Start Antiretroviral Therapy

- The Panel provides information related to the recent report of "functional cure" in an HIV-infected child in Mississippi, discusses the lack of pharmacokinetic (PK) and safety data for most drugs in preterm infants and infants aged <2 weeks, recommends that providers considering treatment for these groups contact a pediatric HIV expert for guidance, and notes that if early treatment is initiated and a child is shown to be infected, the Panel does not recommend empiric treatment interruption unless the durability of the findings in the Mississippi baby can be replicated. In addition, the Panel recommends initiation of cART in children of all ages with HIV RNA levels >100,000 copies/mL **(AII)**.

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

- This section has been reorganized, and some content has been moved to a new, separate section about what drugs should not be started in ARV-naive children.

- Once-daily darunavir in combination with ritonavir is now recommended as a component of a once-daily regimen in adolescents aged ≥12 years.
- Raltegravir, an integrase strand inhibitor (INSTI), is now considered as an agent for Use in Special Circumstances for initial therapy in a cART regimen for ARV-naive pediatric patients despite limited data in children, because of its favorable safety profile, lack of significant drug interactions, and palatability.
- The Panel suggests that clinically stable children with undetectable viral load and stable CD4 counts for more than 6 months can switch from twice-daily to once-daily abacavir as a component of a once-daily regimen.
- The Panel modified its recommendation for fosamprenavir in combination with ritonavir in children aged ≥6 months from "Alternative Option" to "Use in Special Circumstances" due to concerns about the required volume of the liquid formulation and the availability of other Alternative regimens without such problems.
- A section has been added on special considerations for treatment of premature infants and infants younger than age 15 days, discussing lack of PK data to define appropriate dosing in this age group, and consultation with a pediatric expert is recommended if providers consider treating such infants.

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

- A new table has been added summarizing the rationale for not recommending specific ARV regimens or components for initial therapy (see Table 8).

Management of Children Receiving Combination Antiretroviral Therapy

- The former section on "Management of Treatment-Experienced Infants, Children, and Adolescents Receiving Antiretroviral Therapy" has been retitled and restructured into 3 sections:
    1) Modifying ARV regimens in children on effective cART for simplification or improved adverse effect profile
    2) Recognizing and managing treatment failure
    3) Considerations about interruptions in therapy.
- New guidance and a new table (Table 12) is provided about modifying ARV regimens for reasons of improved pill burden, palatability, tolerability, and use of once-daily dosing in children with sustained virologic suppression on their current regimen. The Panel now recommends that changing to a new regimen should be considered in children who have sustained virologic suppression on their current regimen, in order to facilitate continued adherence and increase safety **(BII)**.
- The Panel has added a recommendation indicating that, outside of the context of a clinical trial, structured interruptions of cART are not recommended in the clinical care of HIV-infected children **(AIII)**.

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

- This section has been expanded to provide graded strength recommendations on evaluating plasma concentrations for ARV treatment-naive and treatment-experienced children.
- Evaluation of plasma concentrations of ARV drugs, while not routinely required in the management of HIV-infected pediatric patients, should be considered in children on ART in the following scenarios: **(BII)**
    - Use of ARV drugs with limited PK data and therapeutic experience in children (e.g., use of efavirenz in children aged <3 years and darunavir with once-daily dosing in children aged <12 years)

- ◦ Significant drug-drug interactions and food-drug interactions
- ◦ Unexpected suboptimal treatment response (e.g., lack of virologic suppression with history of medical adherence and lack of resistance mutations)
- ◦ Suspected suboptimal absorption of the drug
- ◦ Suspected dose-dependent toxicity

- Specific recommendations for monitoring plasma concentrations are provided for use of efavirenz in children aged <3 years and darunavir with once-daily dosing in children aged <12 years.
- Evaluation of the genetic G516T polymorphism of drug metabolizing enzyme cytochrome P450 (CYP450) 2B6 is also recommended for children aged <3 years receiving efavirenz because of the significant association of this polymorphism with drug concentrations **(AII)**.

Antiretroviral Drug Resistance Testing

- Table 17, summarizing recommendations for use of available resistance testing, has been added.

Pediatric Antiretroviral Drug Information

- Updates with new pediatric data are provided when relevant to specific drugs. Subheadings have been added to the Pediatric Use section to enhance the ability to locate specific information.

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

- ◦ **Abacavir:** The Panel provides recommendations on once-daily dosing of abacavir in children. In clinically stable children with undetectable viral loads and stable CD4 cell counts for more than 6 months, switching from twice-daily to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose to maximum of 600 mg once daily) is recommended as part of a once-daily regimen.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

- ◦ **Efavirenz:** The Food and Drug Administration (FDA) has approved efavirenz for use in infants and children aged ≥3 months and weighing ≥3.5 kg. However, the Panel recommends that efavirenz generally not be used in children aged 3 months to <3 years because of insufficient data on dosing, and concerns about the potential for underdosing or excessive exposure associated with the CYP 2B6 genotype. Information is provided about use in children aged 3 months to <3 years, including evaluation of the CYP 2B6 genotype prior to dosing and therapeutic drug monitoring. Instructions have been added about the use of capsules as a sprinkle preparation with food or formula.
- ◦ **Nevirapine:** The Panel provides information on the newly available 100-mg extended release (XR) tablets and nevirapine XR dosing in children aged ≥6 years. Supporting information and consideration of initiating full-dose nevirapine (rather than lead-in dosing) in children are discussed. The Panel recommends that children aged >6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine XR without lead-in dosing as long as plasma RNA is undetectable. A new section has been added to discuss the potential use of nevirapine in HIV-infected infants aged <14 days or in premature infants.

Protease Inhibitors

- ◦ **Atazanavir:** Modifications have been made in the dosing table because the 250-mg dose is no longer achievable with currently available capsule dose strengths; 100-mg capsules have been discontinued. The panel discusses new dosing recommendations and notes that some experts would increase the atazanavir dose to 300 mg for children weighing ≥35 kg to avoid underdosing, especially when administered with tenofovir, which decreases plasma atazanavir concentrations.

- **Darunavir:** In February 2013, the FDA approved once-daily dosing of darunavir in children aged >3 years and weight >10 kg, based on population PK modeling. A pediatric trial evaluating once-daily darunavir with ritonavir dosing in children aged 6 to <12 years has not been conducted and no efficacy data have been obtained. Therefore, the Panel recommends that once-daily darunavir with ritonavir should be used only in treatment-naive and treatment-experienced adolescents aged ≥12 years without darunavir resistance-associated mutations. Twice-daily dosing of darunavir with ritonavir should continue to be used in children aged >3 years and <12 years.

Integrase Strand Transfer Inhibitors

- **Dolutegravir:** Information has been added on dolutegravir, which is now FDA-approved for use in adults and children aged ≥12 years and weight ≥40 kg who are treatment-naive or treatment-experienced and integrase strand transfer inhibitor (INSTI)-naive. The Panel notes that dolutegravir is not approved for use in children aged <12 years, but that a clinical trial in treatment-experienced children aged <12 years is under way.
- **Raltegravir:** Raltegravir is now available as an oral suspension that has been FDA-approved for use in infants and children aged ≥4 weeks and weighing 3 kg to <20 kg. This formulation is supplied as a single-use packet to be reconstituted and used within 30 minutes of mixing; unused solution should be discarded.

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

Introduction (Last updated February 12, 2014; last reviewed February 12, 2014)

These guidelines address the use of combination antiretroviral therapy (cART) for HIV-infected infants, children, and adolescents (through puberty). Included is information on management of adverse events associated with use of antiretroviral (ARV) drugs in children and details on pediatric data related to ARV agents. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 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.

Also available on the AIDS*info* website are separate sets of guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children[1] and for the use of ARV agents in HIV-infected (postpubertal) adolescents and adults.[2] Because these guidelines are developed for the United States, they 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.

Advances in medical management, based on results of clinical trials of cART in children, have dramatically reduced morbidity and mortality in HIV-infected children in the United States since the guidelines were first developed in 1993 (with the support of the François-Xavier Bagnoud Center, Rutgers, the State University of New Jersey). HIV mortality has decreased by more than 80% to 90% since the introduction of protease inhibitor (PI)-containing combinations and opportunistic and other related infections have significantly declined in the era of cART.[3,4] Resistance testing has enhanced the ability to choose effective initial regimens as well as second- or third-line regimens. Therapeutic strategies continue to focus on timely initiation of ARV 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 are associated with better adherence and outcomes. The use of ARV drugs in HIV-infected pregnant women has resulted in a dramatic decrease in the rate of HIV transmission to infants in the United States, to less than 2%. The number of infants with AIDS in the United States continues to decline because of the low rate of new infant HIV infections and the availability of cART to prevent AIDS in HIV-infected infants.[5,6] 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 potential for long-term complications from HIV and its treatments.

The pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of cART are similar for all HIV-infected people, 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 age 18 months;
- Age-specific differences in interpreting CD4 T lymphocyte (CD4) cell counts;
- Higher viral loads in perinatally-infected infants compared to HIV-infected adolescents and adults;
- Changes in pharmacokinetic (PK) parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;

- Differences in the clinical manifestations and treatment of HIV infection secondary to onset of infection in growing, immunologically immature individuals; and
- Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

These recommendations represent the current state of knowledge regarding the use of ARV drugs in children and are based on published and unpublished data regarding the treatment of HIV infection in infants, children, adolescents, and adults, and when no definitive data were available, on the clinical expertise of the Panel members. The Panel intends the 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-1-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 U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the 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
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 Health Resources and Services Administration
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 and votes on all proposals during monthly teleconferences. Proposals endorsed by a consensus of members are included in the guidelines as official Panel recommendations.

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 through puberty. For more detailed discussion of issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of cART in HIV-infected pregnant women and interventions for prevention of perinatal transmission, cART 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 efficacy data from adult trials in addition to safety and PK data in children, recommendations for ARV drugs may need to 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.[7]

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

In the absence of large pediatric randomized trials, adult data may be used if there are substantial pediatric data consistent with high-quality adult studies.

- Quality of Evidence Rating I will be used if there are data from large randomized trials <u>in children</u> with clinical and/or validated laboratory endpoints.

- Quality of Evidence Rating I* will be used if there are high-quality randomized clinical trial data in adults with clinical and/or validated laboratory endpoints and pediatric data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes that are consistent with the adult studies. A rating of I* may be used for quality of evidence if, for example, a randomized Phase III clinical trial in adults demonstrates a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

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

In the absence of large, well-designed, pediatric, nonrandomized trials or observational data, adult data may be used if there are sufficient pediatric data consistent with high-quality adult studies.

- 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

References

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Identification of Perinatal HIV Exposure (Last updated February 12, 2014; last reviewed February 12, 2014)

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 should be considered for all HIV-seronegative pregnant women and is recommended for pregnant women who are at high risk of HIV infection **(AIII)**. • Rapid or expedited HIV testing at the time of labor or delivery should be performed on women with undocumented HIV status; if results are positive, intrapartum and infant postnatal antiretroviral (ARV) prophylaxis should be initiated immediately, pending results of the confirmatory HIV antibody test **(AII)**. • Women who have not been tested for HIV before or during labor should undergo rapid or expedited HIV testing during the immediate postpartum period or their newborns should undergo rapid HIV testing. If results in mother or infant are positive, infant ARV prophylaxis should be initiated as soon as possible and the mothers should not breastfeed unless confirmatory HIV antibody testing is negative **(AII)**. • For HIV-seronegative women in whom acute HIV infection is suspected during pregnancy, intrapartum, or while breastfeeding, a virologic test (e.g., plasma HIV RNA assay, antigen/antibody combination immunoassay) should be performed because serologic testing may be negative at this early stage of 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*

In order to best prevent infant HIV infection and start therapy as soon as possible in those who become infected, HIV infection should be identified as early in pregnancy as possible. Universal HIV counseling and voluntary HIV testing are 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 U.S. Public Health Service (USPHS), the American Academy of Pediatrics (AAP), 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. The Centers for Disease Control and Prevention (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-in" approach involves obtaining specific consent before testing and has been associated with lower testing rates. The mandatory newborn HIV testing approach involves testing of newborns for perinatal HIV exposure with or without maternal consent.

Early identification of HIV-infected women is crucial for their health and for the care of their children, whether the children are infected or not. Knowledge of antenatal maternal HIV infection enables:

- HIV-infected women to receive appropriate combination antiretroviral therapy (cART) and prophylaxis against opportunistic infections for their own health, which may also decrease risk of transmission to their partners[4,7,8]

- Providing cART to the mother during pregnancy and labor, and antiretroviral (ARV) prophylaxis to the newborn to reduce the risk of perinatal transmission of HIV transmission;[6]
- Counseling HIV-infected women about the indications for (and potential benefits of) scheduled cesarean delivery to reduce perinatal transmission of HIV;[6,9-11]
- Counseling HIV-infected women about the risks of HIV transmission through breast milk and that breastfeeding is not recommended for HIV-infected women living in the United States and other countries where safe alternatives to breast milk are available;[12]
- 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;[13] and
- Early diagnostic evaluation of HIV-exposed infants, as well as testing of partners and other children to permit prompt initiation of cART in infected individuals.[1,14]

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, preferably before 36 weeks' gestation, is recommended[6,15] 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 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);
- 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 1 sex partner during current pregnancy, or have been diagnosed with a new sexually transmitted disease during pregnancy); or
- Have signs or symptoms of acute HIV infection.[4,5,16]

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. There is evidence that for women, the risk of HIV acquisition is significantly higher during pregnancy than in the postpartum period.[17] If acute HIV infection is a possibility, virologic testing with a plasma HIV RNA assay or, if unavailable, an antigen/antibody combination immunoassay should be performed because serologic testing may be negative at this early stage of infection.[18]

Rapid HIV Testing During Labor in Women with Unknown HIV Status

Use of rapid test kits or an expedited immunoassay to detect HIV infection is recommended to screen women in labor whose HIV status is undocumented and identify HIV exposure in their infants.[1,4,5,14,19] Any hospital offering intrapartum care should have rapid or expedited HIV testing available and should have policies and procedures in place to ensure that staff are prepared to provide patient education about rapid or expedited HIV testing, that results are available ideally within one hour, that appropriate ARV medications are available whenever needed, and that follow-up procedures are in place for women found to be HIV-infected and their infants. Rapid tests have 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.[20] Results of rapid tests can be obtained within minutes to a few hours with accuracy comparable to standard enzyme-linked immunosorbent assays (EIA).[19,21,22] A single negative rapid test does not need confirmation unless acute HIV infection is a possibility, in which case, a virologic test is necessary.[18] A positive rapid HIV test result must be followed by a supplemental test to confirm the prescence of HIV infection.[22] However, immediate initiation of ARV prophylaxis for prevention of perinatal transmission of HIV is strongly recommended pending confirmation of an initial positive rapid HIV test.[1,3,6,14]

HIV Counseling and Testing During the Postnatal Period

Women who have not been tested for HIV before or during labor should be offered rapid or expedited testing during the immediate postpartum period or their newborns should undergo rapid or expedited HIV testing with maternal consent (unless state law allows testing without consent).[1,5,6,14] Use of rapid or expedited HIV assays or expedited EIA 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 12 hours later—to be effective for the prevention of perinatal transmission. When an initial HIV test is positive in mother or infant, initiation of infant ARV prophylaxis and counseling against initiation of breastfeeding is strongly recommended pending results of confirmatory HIV tests.[6] If confirmatory tests are negative and acute HIV infection is excluded, infant ARV 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 Unavilable

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 the infant.[1] If antibody testing is positive, further testing is needed to diagnose HIV infection, or in the case of infants aged >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.[23-25] When acute retroviral syndrome is a possibility in pregnancy or during breastfeeding, maternal testing should include a combination antigen/antibody immunoassay or plasma HIV RNA test, because HIV antibody testing may be negative in early maternal infection. Women with possible acute HIV infection who are breastfeeding should stop breastfeeding immediately until HIV infection is confirmed or excluded.[12] 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 and their infants identified with acute or early HIV infection should follow guidelines in the Perinatal Guidelines.[6]

Surveillance Reporting of HIV Exposed Infants to Local and State Health Departments

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 February 12, 2014; last reviewed February 12, 2014)

Panel's Recommendations
• Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months **(AII)**. • HIV DNA polymerase chain reaction and HIV RNA assays are recommended as preferred virologic assays **(AII)**. • Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months **(AII)**. • Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection **(BIII)**. • Virologic diagnostic testing should be considered 2 to 4 weeks after cessation of antiretroviral (ARV) prophylaxis for infants receiving combination ARV infant prophylaxis, if the results of prior virologic testing were negative while the infant was receiving prophylaxis **(BIII)**. • A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**. • Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with one obtained at age ≥1 month and one 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 infants with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**. • Screening HIV antibody assays in conjunction with a confirmatory antibody test or virologic detection test can be used for diagnosis of HIV infection in children with perinatal exposure aged ≥18 months and in children with non-perinatal exposure (see text for special situations) **(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*

Diagnostic Testing in Infants with Perinatal HIV-1 (HIV) Exposure

HIV infection can be definitively diagnosed through use of virologic assays in most non-breastfed HIV-exposed infants by age 1 month and in virtually all infected infants by age 4 months. Tests for antibodies to HIV, 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 amplification tests [NAT]—a class of tests which includes HIV DNA, RNA 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.

HIV culture is not used for routine HIV diagnostic testing, although it has sensitivity similar to that of HIV DNA PCR.[3] It is more complex and expensive to perform than DNA PCR or RNA assays, requires 2 to 4 weeks for definitive results, and is generally not available outside of research laboratories. Use of the currently approved HIV p24 antigen assay is not recommended for infant diagnosis in the United States because the sensitivity and specificity of the assay in the first months of life are less than that of other HIV virologic tests.[4,5]

Infants who are found to have positive HIV antibody tests on screening 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.[6]

HIV DNA PCR

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 1, 3, and 6 months. The sensitivity of the test performed at birth is 55% but increases to more than 90% by 2 to 4 weeks of age, and 100% at ages 3 months and 6 months.[6-9]

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, 1, 3, and 6 months of age and is comparable to HIV DNA PCR.[8] HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before they are interpreted as documenting HIV infection in an infant. The sensitivity of HIV RNA assays has been shown to be 25% to 58% during the first weeks of life, 89% at age 1 month, and increases to 90% to 100% by age 2 to 3 months.[6-8,10-12] In studies of infants receiving zidovudine or no prophylaxis, HIV RNA assays were found to be as sensitive as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants. An HIV RNA assay can be used as the confirmatory 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 HIV Subtype section below). While HIV DNA PCR remains positive in most individuals receiving antiretroviral treatment, HIV RNA assays may be affected by maternal antenatal treatment or infant combination antiretroviral (ARV) prophylaxis.[8,13] 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 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. These data suggest that diagnostic sensitivity of HIV assays may be affected by the type of infant prophylaxis.[8] Further studies are necessary to confirm this trend.

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing.[9,14-18]

Issues Related to Diagnosis of 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, 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.[19-22] Geographical distribution of HIV groups is available at http://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp.

Currently available 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.[23-25] In an evaluation of perinatally infected infants diagnosed in New York State in 2001 through 2002, 16.7% of infants were infected with a non-subtype B strain of HIV, compared with 4.4% of infants diagnosed between 1998 and 1999.[26]

Currently available real-time HIV RNA PCR assays have improved sensitivity for detection of non-subtype B HIV infection and the more uncommon Group O strains compared to other RNA assays that do not detect or properly quantify all non-B subtypes and group O HIV[27-32] (see HIV RNA Monitoring in Children:

General Considerations in Clinical and Laboratory Monitoring).

When evaluating an infant whose mother or father (or both) comes from an area endemic for non-subtype B HIV or Group O strains, such as Africa and Southeast Asia, clinicians should consider conducting initial testing using one of the assays more sensitive for non-subtype B viruses, such as one of the real-time PCR assays. In addition, when non-subtype B perinatal exposure is suspected in infants with negative HIV DNA PCR results, repeat testing using one of the newer RNA assays is recommended. The child should undergo close clinical monitoring and HIV serologic testing at age 18 months 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.

Issues Related to Diagnosis of HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique;West African countries including Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and in parts of India.[33,34] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions;[35,36] HIV-2 is rare in the United States. HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic, who are HIV-1 antibody-positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot and HIV-1 RNA viral loads at or below the limit of detection.[37,38] This pattern of HIV testing can also be seen in patients who have a false-positive HIV-1 test. HIV-1 and HIV-2 coinfections may also occur, further complicating the diagnosis.

The majority of commercially available HIV screening antibody tests can detect both HIV-1 and HIV-2 but cannot distinguish between the two viruses. The only Food and Drug Administration (FDA)-approved antibody test that distinguishes between HIV-1 and HIV-2 is the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test. If HIV-2 is suspected, infection can be confirmed using a supplemental test such as an HIV-2 immunoblot or HIV-2-specific Western blot. HIV-2 immunoblots are available through commercial labs; however, none are FDA-approved for HIV-2 diagnosis. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by their public health laboratory or the CDC.

Infants born to HIV-2-infected mothers should be tested for HIV-2 infection with HIV-2-specific virologic assays (HIV-2 DNA PCR testing) at time points similar to those used for HIV-1 testing. HIV-2 virologic assays are not commercially available, but the National Perinatal HIV Hotline (1-888-448-8765) can provide a list of sites that perform this testing. Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[34,39-41]

Timing of Diagnostic Testing in Infants with Known Perinatal HIV Exposure

Virologic diagnostic testing of an HIV-exposed infant should be performed at age 14 to 21 days, at age 1 to 2 months, and at age 4 to 6 months. Virologic diagnostic testing should be considered at birth for infants at high risk of HIV infection and 2 to 4 weeks after discontinuation of prophylaxis for infants receiving combination neonatal ARV regimens (see below).

Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples, regardless of a child's age. A positive HIV antibody test with confirmatory Western blot (or immunofluorescent antibody [IFA] assay) at age ≥18 months confirms HIV infection, except in occasional late seroreverters (see the *Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations* section below).[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 at age ≥8 weeks, or one negative HIV antibody test at age ≥6 months.[1,6] *Pneumocystis jiroveci* 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.[42,43] Thus, initiation of PCP prophylaxis can be avoided or discontinued if an infant has negative virologic tests at ages 2 weeks and ≥4 weeks, or if virologic testing is negative at age ≥8 weeks.

Definitive exclusion of HIV infection in a non-breastfed infant is based on 2 or more negative virologic tests, 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.[44] As many as 30% to 40% of HIV-infected infants can be identified by age 48 hours.[6] 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 for diagnostic evaluations because of the potential for contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection during the intrauterine period 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.[45] Some researchers have proposed that infants with early infection may have more rapid disease progression than those with late infection and, therefore, should receive more aggressive therapy.[45,46] However, data from prospective cohort studies have demonstrated that although early differences in HIV RNA levels were present between infants with a positive HIV culture within 48 hours of birth and those with a first positive culture after age 7 days, these differences were no longer statistically significant after age 2 months.[47] HIV RNA levels after the first month of life were more predictive of rapid disease progression than the time at which HIV culture tests were positive.[47,48]

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks[6] and early identification of infection would permit discontinuation of neonatal ARV prophylaxis and further evaluation for initiation of ARV therapy (see Infants Younger than Age 12 Months and Table 5 in When to Initiate).

Virologic Testing at Age 1 to 2 Months

Infants with negative virologic tests before age 1 month should be retested at age 1 to 2 months. Most HIV-exposed neonates will receive 6 weeks of neonatal ARV prophylaxis. 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 (PACTG) protocol 076 or the sensitivity and predictive values of many virologic assays,[6,10-12,49] this may not always apply to current combination prenatal and neonatal ARV regimens if the test is obtained while the infant is receiving combination neonatal ARV prophylaxis.[8]

Virologic diagnostic testing for infants receiving combination ARV infant prophylaxis should be considered 2 to 4 weeks after cessation of prophylaxis if prior negative diagnostic testing was performed during the period of prophylaxis. In such situations, the test recommended at age 1 to 2 months can be delayed until after cessation of ARV prophylaxis.

An infant with two negative virologic tests, one at age ≥14 days and one at age ≥1 month, 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 evidence of HIV infection.

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.[50] 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.[50-53]

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

- Late seroreversion up to age 24 months
- Postnatal HIV infection in HIV-exposed children with prior negative virologic tests for whom there are additional HIV transmission risks
- HIV-2 and non-subtype B HIV-1

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 for up to age 24 months (these infants are called late seroreverters).[52-55] In one study 14% seroreverted after age 18 months.[50] These children may have positive enzyme-linked immunosorbent assay (EIA) results but indeterminate confirmatory antibody tests (Western Blot or IFA). In such cases, repeat antibody testing at a later time would document seroreversion.

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). If a confirmatory HIV antibody test is positive at age 18 months, repeated virologic testing will distinguish between residual antibodies in uninfected, late seroreverting children and true infection.

Postnatal HIV exposure can occur if an HIV-infected mother breastfeeds her infant. 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, and women who learn of their HIV diagnosis only after initiating breastfeeding. Diagnostic testing to rule out acquisition of HIV through breast milk will only be accurate after breastfeeding has completely ceased. The timing of testing in such situations is discussed below in Diagnostic Testing in Children with Non-Perinatal HIV Exposure.

Another example where there can be postnatal HIV exposure is when an HIV-infected caregiver premasticates or prechews solid food before feeding it to an infant. This practice has been documented to result in HIV transmission.[41,54-58] In such exposed children, both screening EIA and confirmatory antibody tests (EIA, Western Blot or IFA) may be positive at 18 months. Another study documented very rare cases of late postnatal infection without identified risk factors, suggesting the possibility of intrafamilial HIV transmission.[59]

Children with non-subtype B HIV-1 infection and children with HIV-2 infection may have persistent positive EIA tests and indeterminate confirmatory antibody tests.[23-25,60] Situations in which such infections may be suspected and the diagnostic approach to them are discussed above in Issues Related to Diagnosis of Group M Non-Subtype B and Group O HIV-1 Infections and Issues Related to Diagnosis of HIV-2 Infection.

Diagnostic Testing in Children with Non-Perinatal HIV Exposure

Breastfeeding is a known route of HIV transmission. Infants who are breastfed by HIV-infected women, including those diagnosed with acute HIV infection during breastfeeding or who breastfed before knowing their HIV diagnosis should undergo immediate HIV virologic testing and breastfeeding should be discontinued. Follow-up virologic testing should be performed at 4 to 6 weeks, 3 and 6 months after breastfeeding cessation if the initial tests are negative.[61,62] HIV antibody testing of an infant to assess for HIV exposure would not be helpful if the mother acquired HIV infection after giving birth. In that situation, an infant would be HIV antibody-negative but still at risk of acquiring HIV infection through breastfeeding and counseling to cease breastfeeding should be provided.

Perinatal HIV acquisition accounts for the majority of HIV infections in children, but providers may need to evaluate children exposed to HIV through other routes, such as sexual abuse, or because they were adopted from countries in which parenteral exposure to HIV via contaminated blood products is a possibility. In such cases, maternal HIV status may be negative or unknown. Receipt of solid food premasticated or prechewed by an HIV-infected caregiver also has been documented to be associated with risk of HIV transmission.[41,54-58] Finally, acquisition of HIV is possible through accidental needlesticks or behavioral risks, such as sexual activity or injection drug use in older children.

Screening HIV antibody assays in conjunction with a confirmatory antibody test or virologic detection test should be performed on children who are suspected to have HIV infection because of clinical or laboratory findings consistent with HIV. Additional virologic testing may be necessary if acute HIV infection or end-stage AIDS is suspected because antibody testing can be negative in these situations.

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Clinical and Laboratory Monitoring of Pediatric HIV Infection (Last updated February 12, 2014; last reviewed February 12, 2014)

Panel's Recommendations
• CD4 T lymphocyte (CD4) percentage is generally preferred for monitoring immune status in children younger than age 5 years because of age-related changes in absolute CD4 cell count; however, absolute CD4 count may also be used **(AII)**. • CD4 cell count/percentage and plasma HIV RNA (viral load) should be measured at the time of diagnosis of HIV infection and at least every 3 to 4 months thereafter for children not on combination antiretroviral therapy (cART) **(AIII)**. • More frequent CD4 cell count/percentage and plasma viral load monitoring should be considered in children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value **(AIII)**. • After initiation of cART (or after a change in cART 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 2-4 weeks after treatment initiation **(AIII)**. • Children on cART should have evaluation of therapy adherence, effectiveness (by CD4 cell count/percentage and plasma viral load), and toxicities (by history, physical, and selected laboratory tests) routinely be assessed every 3 to 4 months **(AII*)**. • CD4 cell count/percentage 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 **(BII)**.
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 varies significantly by age. This section will address immunologic, virologic, and general laboratory monitoring of HIV-infected children, relevant to both those who are and are not receiving combination antiretroviral therapy (cART).

Immunologic Monitoring in Children: General Considerations

Clinicians interpreting CD4 cell count and percentage in children must consider age as a factor. CD4 cell count and percentage values in healthy infants who are HIV-uninfected are considerably higher than values observed in uninfected adults and slowly decline to adult values by age 5 years.[1,2] 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 generally been preferred for monitoring immune status, whereas absolute CD4 cell count has been the preferred option for children aged ≥5 years, although CD4 cell count can be used in younger children if CD4 percentage is not available.[3-5] An analysis from the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) 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,[6] and either or both can be used in decisions on when to initiate cART (see When to Initiate).

In HIV-infected children, as in infected adults, the CD4 cell count and percentage decline as HIV infection progresses and 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.[4] The 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).[3,7]

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 six fold 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 or older 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 or older 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).

These risk profiles contribute to the rationale 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 HPPMCS is available to estimate the short-term risk of progression to AIDS or death in the absence of effective cART according to age and the most recent CD4 percentage/absolute CD4 cell count or HIV-1 RNA viral load measurement (http://hppmcs.org).[4]

Measurement of CD4 cell count and percentage can be associated with considerable intrapatient variation.[5] Mild intercurrent illness or the receipt of vaccinations 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.[8,9] 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.[10]

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.[11,12] In one prospective study of infants with perinatal infection born prior to antiretroviral (ARV) 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.[13] After the first year of life, plasma viral load slowly declined over the next few years.[13-16] 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.[17]

High plasma viral load (i.e., >299,000 copies/mL) in infants younger than age 12 months has been correlated with disease progression and death, but the range of plasma viral loads overlap considerably in young infants who have rapid disease progression and those who do not.[11,13] 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).[15,16] The most robust data set available to elucidate the predictive value of plasma viral load for disease progression in children was assembled in the HPPMCS[4] (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 aged 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.[15] 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.[12] 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.[15,16,18,19]

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. 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.[20,21]

Six Food and Drug Administration (FDA)-approved viral load assays using one of four different methodologies currently exist:

- HIV-1 reverse transcriptase (RT) quantitative polymerase chain reaction (PCR) assays: the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics), for which the lower limit of quantification differs between the "ultrasensitive" assay (<50 copies/mL) and the "regular sensitivity" assay (<400 copies/mL); the AmpliPrep/TaqMan HIV-1 Test, including the COBAS automated format (Roche Diagnostics); and the Real Time HIV-1 Assay (Abbott Molecular Incorporated);
- HIV-1 nucleic acid sequence-based amplification test (NucliSENS EasyQ® HIV-1 v2.0, bioMerieux);
- HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay (VERSANT HIV-1 RNA 3.0 Assay [bDNA], Siemens); and
- Aptima HIV-1 RNA Qualitative assay (Gen-Probe Inc., San Diego, CA), primarily used for HIV diagnosis, as well as detection of less than full viral suppression during therapy.

The lower limits of quantification of the assays differ (less than 40 copies/mL for the Abbott Real Time HIV-1 test, less than 20 copies/mL for the AmpliPrep/TaqMan HIV-1 Test/Version 2, less than 50 copies/mL for the Amplicor HIV-1 Monitor Test, less than 20 copies/mL for the NucliSENS EasyQ® HIV-1 v2.0, and less than 50 copies/mL for the VERSANT assay). Use of ultrasensitive viral load assays is recommended to confirm that cART is producing maximal suppression of viremia. Because of the variability among assays in techniques and quantitative HIV RNA measurements, if possible, a single HIV RNA assay method should be used consistently to monitor an individual patient.[22-24]

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.[25,26] 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.[22,27-31] 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 µL of plasma), followed by the RT-PCR assays such as the Amplicor HIV-1 Monitor (200 µL of plasma) and VERSANT assays (1 mL 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.[18,21] 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 age 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 substantial.

No clinical decisions 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).[32] Temporary viral load elevations (“blips”) between the level of detection and 500 copies/mL often are detected in adults[33] and children on cART 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.

Clinical and Laboratory Monitoring of Children with HIV Infection

Table 3 provides one proposed general monitoring schedule, which should be adjusted based on the specific cART regimen a child is receiving.

Entry into Care—Baseline Evaluation

At entry into care, HIV-infected children should have a complete age-appropriate medical history, physical examination, and laboratory evaluation (see Table 3). This should include a general medical and social history (e.g., immunizations, nutrition, physical and social environment), evaluation for HIV-specific physical conditions (e.g., growth delay, microcephaly, motor or cognitive neurologic problems), evaluation for HIV-associated laboratory abnormalities (e.g., anemia, leukopenia, thrombocytopenia, elevated glucose, transaminases or creatinine, hypoalbuminemia), and assessment of presence or risk of opportunistic infections (see the Pediatric Opportunistic Infections Guidelines).

Laboratory confirmation of HIV infection should be obtained if available documentation is incomplete (see Diagnosis of HIV Infection). CD4 cell count and percentage, as well as plasma HIV RNA measurements (i.e., viral load), should be obtained at entry into care to help guide decisions about timing of cART initiation (see When to Initiate). Genotype resistance testing should be performed, even if cART is not initiated immediately. For patients previously treated with ARV drugs, resistance evaluation requires a complete ARV history (see Antiretroviral Drug-Resistance Testing).

Monitoring of Children Not Receiving Antiretroviral Therapy

Children not receiving cART should be evaluated every 3 to 4 months with measurement of CD4 cell count and percentage, 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, or creatinine, and hypoalbuminemia. Urinalysis should be obtained every 6 to 12 months to monitor for HIV-associated nephropathy. Opportunistic infection monitoring should follow guidelines appropriate for the child's exposure history and clinical setting (see the Pediatric Opportunistic Infections Guidelines).

More frequent evaluation may be necessary for children experiencing virologic, immunologic, or clinical deterioration or to confirm an abnormal value.

Initiation of Combination Antiretroviral Therapy—Overview

Readiness for ARV adherence should be assessed prior to starting cART. If abacavir is being considered as part of the regimen, HLA-B*5701 testing should be sent prior to initiation of that ARV, and an alternative ARV should be used 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).

Children who start cART or who change to a new regimen should be followed to assess effectiveness, tolerability, and side effects of the regimen and to evaluate medication adherence. Frequent patient visits and intensive follow-up during the initial months after a new ARV regimen is started are necessary to support and educate the family. The first few weeks of cART can be particularly difficult for children and their caregivers; they must adjust their schedules to allow for consistent and routine administration of medication doses. Children may also experience side 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.

Monitoring of Children Receiving Antiretroviral Therapy

Evaluations at Initiation of cART

At the time of cART initiation, CD4 cell count and percentage and plasma viral load should be measured to establish a baseline to monitor cART benefit. To set the baseline for monitoring cART 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 fumerate, creatinine may increase, phosphate decrease, and proteinuria can occur (see Tenofovir 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). Some practitioners measure baseline creatine kinase before starting zidovudine (see Zidovudine in Appendix A: Pediatric Antiretroviral Drug Information) or raltegravir (see Raltegravir in Appendix A: Pediatric Antiretroviral Drug Information). For further details of adverse effects associated with a particular ARV, see Tables 11a-11l in Management of Medication Toxicity or Intolerance.

Within 1 to 2 Weeks of Initiation of cART

Within 1 to 2 weeks of initiating therapy, children should be evaluated either in person or by phone to identify clinical side effects and to support adherence. Many clinicians plan additional contacts (in person or by telephone) with children and caregivers to support adherence during the first few weeks of therapy.

2 to 4 Weeks after Initiation of cART

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 cART to assess virologic response and laboratory toxicity. Laboratory chemistry tests to measure are 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 cART 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 cART initiation may be slower than in adults. A significant decrease in viral load in response to cART should be observed by 4 to 8 weeks of therapy.

Routine Testing for Patients Receiving Combination Antiretroviral Therapy

After the initial phase of cART initiation, regimen adherence, effectiveness (CD4 cell count and percentage and plasma viral load), and toxicities (history, physical, and laboratory testing as above) should be assessed every 3 to 4 months in children receiving cART. Children who develop symptoms of toxicity should have appropriate laboratory evaluations (such as evaluation of serum lactate in a child receiving NRTIs who develops symptoms suspicious for lactic acidosis). If laboratory evidence of toxicity is identified, testing should be performed more frequently until the toxicity resolves.

Testing for Patients Who are Stable on Long-Term cART

Some experts monitor CD4 cell count and percentage 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. 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.[34-39] 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 cART

When a switch in regimen is made to simplify cART, 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 regimen is switched because of cART 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).

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

	Entry Into Care[1]	Pre-Therapy[2]	cART 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 / Percentage	√	√	√			√		√
Plasma Viral Load	√	√	√		√	√		√
Resistance Testing	√							√
CBC with Differential	√	√	√		√	√		√
Chemistries	√	√	√		√	√		√
Lipid Panel	√		√				√	
Urinalysis	√		√				√	

[1] See text for details of appropriate tests to send.

[2] Readiness for ARV adherence is assessed prior to starting cART. 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). Send tests appropriate to the toxicities expected from each patient's cART regimen and history (see text).

[3] If cART is initiated within 30 to 45 days of a pre-therapy lab result, repeat testing may not be necessary.

[4] CD4 cell count and percentage can be monitored less frequently (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.

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

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, CBC = complete blood count

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Treatment Recommendations (Last updated February 12, 2014; last reviewed February 12, 2014)

General Considerations

Antiretroviral (ARV) treatment of pediatric HIV infection has steadily improved with the introduction of potent combination drug regimens that effectively suppress viral replication in most patients, resulting in a lower risk of failure due to development of drug resistance. Currently, combination antiretroviral treatment (cART) 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.[1-5] In the United States and the United Kingdom, significant declines (81%–93%) in mortality have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of highly active combination regimens;[6-8] significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period.[4,7] As a result, some perinatally HIV-infected children are now living into the third and fourth decades of life, and potentially, 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[9-12] (see Management of Medication Toxicity or Intolerance).

ARV drug-resistant virus can develop during cART because of poor adherence, a regimen that is not potent, or a combination of these factors which results in incomplete viral suppression. In addition, primary drug resistance may be seen in ARV-naive children who have become infected with a resistant virus.[13-15] Thus, decisions about when to start therapy (see When to Initiate), 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.

Several factors need to be considered in making decisions about initiating and changing cART in children, including:

- Severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or AIDS-defining illnesses (see Centers for Disease Control and Prevention (CDC) pediatric clinical staging system for HIV http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm),[16] degree of CD4 T lymphocyte (CD4) immunosuppression, 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 group;
- Potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the cART regimen;
- Effect of initial regimen choice on later therapeutic options;
- A child's cART 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 drug choice;
- Potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a child; and

- The 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

Although there is a single case report of "functional cure" in an HIV-infected child treated with a cART regimen initiated at age 30 hours,[17] current cART does not eradicate HIV infection in the majority of perinatally infected infants because of the long half-life of latently infected CD4 cells.[18-20] 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).[21] Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of cART for HIV-infected children and adolescents include:

- Reducing HIV-related mortality and morbidity;
- 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 complex balancing of sometimes competing considerations.

Use and Selection of cART

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

Maximizing Adherence

As discussed in Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents, poor adherence to prescribed regimens can lead to subtherapeutic levels of ARV medications, which enhances 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 the decision to initiate therapy is made. Participation by the caregiver and child in the decision-making process is crucial. Potential problems should be identified and resolved before starting therapy, 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 before making changes to the cART regimen.

Table 4. 1994 Revised HIV Pediatric (Age <13 Years) Classification System: Clinical Categories*
(page 1 of 2)

Category N: Not Symptomatic
Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.
Category A: Mildly Symptomatic
Children with **two** or more of the following conditions but none of the conditions listed in Categories B and C: • Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral = 1 site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent or persistent upper respiratory infection, sinusitis, or otitis media
Category B: Moderately Symptomatic
Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following: • Anemia (<8 g/dL), neutropenia (<1,000 cells/mm^3), or thrombocytopenia (<100,000 cells/mm^3) persisting ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children aged >6 months • Cardiomyopathy • Cytomegalovirus infection with onset before age 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than 2 episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month • Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex • Nephropathy • Nocardiosis • Fever lasting >1 month • Toxoplasmosis with onset before age 1 month • Varicella, disseminated (i.e., complicated chickenpox)

Table 4. 1994 Revised HIV Pediatric (Age <13 Years) Classification System: Clinical Categories* (page 2 of 2)

Category C: Severely Symptomatic
Children who have any condition listed in the 1987 surveillance case definition for AIDS (below), with the exception of LIP, which is a Category B condition: • Serious bacterial infections, multiple or recurrent (i.e., any combination of at least 2 culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections) • Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs) • Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes) • Cryptococcosis, extrapulmonary • Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month • Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes) • Encephalopathy—at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings: ◦ Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests ◦ Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children aged <2 years) ◦ Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance • HSV infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child aged >1 month • Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes) • Kaposi sarcoma • Lymphoma, primary, in brain • Lymphoma, small, noncleaved cell (Burkitt), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype • *Mycobacterium tuberculosis*, disseminated or extrapulmonary • Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes) • *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes) • *Pneumocystis jirovecii* pneumonia • Progressive multifocal leukoencephalopathy • Salmonella (nontyphoid) septicemia, recurrent • Toxoplasmosis of the brain with onset at age >1 month • Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: ◦ Persistent weight loss >10% of baseline; **<u>or</u>** ◦ Downward crossing of at least two of the following percentile lines on the weight-for-age chart (such as 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; **<u>or</u>** ◦ <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart **<u>plus</u>** ◦ Chronic diarrhea (that is, ≥2 loose stools per day for >30 days) **<u>or</u>** documented fever (for ≥30 days, intermittent or constant)

* 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): p. 1–10.

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When to Initiate Therapy in Antiretroviral-Naive Children (Last updated February 12, 2014; last reviewed February 12, 2014)

Overview

The decision about when to initiate combination antiretroviral therapy (cART) in asymptomatic HIV-infected older children, adolescents, and adults continues to generate controversy among HIV experts. Aggressive therapy in the early stages of HIV infection has the potential to control viral replication before the evolution of HIV in that individual into a diverse and potentially more pathogenic quasispecies. Initiation of therapy at higher CD4 T lymphocyte (CD4) cell counts has been associated with fewer drug resistance mutations at virologic failure in adults.[1] Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression.[2] Ongoing viral replication may be associated with persistent inflammation and development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of replication may reduce the occurrence of these non-AIDS complications.[2-8] 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 cART. Because therapy in children is initiated at a young age and will likely be life-long, concerns about adherence and toxicities are particularly important.

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, with the proviso that the strength of the recommendations is dependent on the pre-treatment CD4 cell count.[9] Randomized clinical trials have provided definitive evidence of benefit with initiation of therapy in adults with CD4 cell counts <350 cells/mm^3.[10] Observational cohort data have demonstrated the benefit of treatment in adults with CD4 cell counts between 350 and 500 cells/mm^3 in reducing morbidity and mortality; therefore, adult treatment guidelines recommend initiation of lifelong cART for individuals with CD4 cell counts ≤500 cells/mm^3.[9,11-14] For adults with CD4 counts >500 cell/mm^3, observational data are less conclusive regarding the potential survival benefit of early treatment.[11,12,15] The recommendation for initiation of therapy at CD4 counts >500/mm^3 (**BIII** evidence) in adults is based on accumulating data that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, the availability of more effective cART regimens with improved tolerability, and evidence that effective cART reduces sexual HIV transmission.[16] However, the Adult Guidelines Panel acknowledges that the amount of data supporting earlier initiation of therapy decreases as the CD4 cell count increases above 500 cells/mm^3, and that concerns remain over the unknown overall benefit, long-term risks, cumulative additional costs, and potential for decreased medication adherence associated with earlier treatment in asymptomatic patients.[9]

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

Panel's Recommendations

- Combination antiretroviral therapy (cART) should be initiated in all children with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions) **(AI*)**.
- cART should be initiated in HIV-infected infants aged <12 months regardless of clinical status, CD4 T lymphocyte (CD4) percentage or viral load (**AI** for infants aged <12 weeks and **AII** for infants aged ≥12 weeks to 12 months).
- cART should be initiated in HIV-infected children aged ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
  - Ages 1 to <3 years
    - With CD4 count <1000 cells/mm^3 or CD4 percentage <25% **(AII)**
  - Ages 3 to <5 years
    - With CD4 cell count <750 cells/mm^3 or CD4 percentage <25% **(AII)**
  - Age ≥5 years
    - With CD4 cell count <350 cells/mm^3 **(AI*)**
    - With CD4 cell count 350–500 cells/mm^3 **(BII*)**
- cART should be considered for HIV-infected children aged ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
  - Ages 1 to <3 years
    - With CD4 cell count ≥1000 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
  - Ages 3 to <5 years
    - With CD4 cell count ≥750 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
  - Age ≥5 years
    - With CD4 cell count >500 cells/mm^3 **(BIII)**
- cART should be initiated in HIV-infected children aged ≥1 year with confirmed plasma HIV RNA levels >100,000 copies/mL **(AII)**.
- Issues associated with adherence should be assessed and discussed with an HIV-infected child's caregivers before initiation of therapy **(AIII)**. 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.

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

Infants Younger Than Age 12 Months

The Children with HIV Early Antiretroviral Therapy (CHER) Trial, a randomized clinical trial in South Africa, demonstrated that initiating triple-drug, cART before age 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.[17] 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.[18] Because the risk of rapid progression is so high in young infants and based on the data in young infants from the CHER study, the Panel recommends initiating therapy for all infants aged <12 months regardless of clinical status, CD4 percentage, or viral load (Table 5). 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 aged <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 age 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[19] 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 aged <12 months.[20] 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 can occur in young infants with normal CD4 cell counts.[20]

Identification of HIV infection during the first few months of life permits clinicians to initiate cART 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.[2,21-24] A study of 195 South African children initiating cART aged <24 months found that infants treated by age 6 months achieved target growth milestones more rapidly than children who initiated therapy between ages 12 and 24 months.[25] 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.[26,27] In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication. Some of these infants have become HIV seronegative. Although there is a single case report of "functional cure" in an HIV-infected child treated with a cART regimen initiated at age 30 hours, discussed below, current cART does not eradicate HIV infection in the majority of perinatally infected infants because of the long half-life of latently infected CD4 cells.[28,29]

A recent report of a "functional cure" in an HIV-infected child in Mississippi has generated discussion about early initiation of cART in newborn infants with high-risk HIV exposure. This newborn, born to a mother who did not receive antenatal or perinatal cART, was treated with a 3-drug cART regimen at ages 30 hours through 18 months, after which cART was discontinued against medical advice. Follow-up evaluations off cART showed no evidence of virologic rebound by standard clinical assays, and although a scant amount of HIV nucleic acid was detected, replication-competent virus was not.[30] 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 antiretroviral (ARV) drugs in infants aged <2 to 4 weeks, drug and dose selection in this age group is challenging (see What to Start). If early treatment is initiated, the Panel does not recommend empiric treatment interruption until the durability of the findings in the Mississippi baby can be studied and replicated in other children.

Virologic suppression may take longer to achieve in young children than in older children or adults.[31,32] 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 age <12 months.[2,33,34] In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at age <6 months, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.[2] 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 lopinavir/ritonavir-based cART before age 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 T-cell pool).[35]

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.[36] 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 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.[37]

Children Aged 1 Year and Older

Disease progression is less rapid in children aged ≥1 year.[19] Children with clinical AIDS or significant symptoms (Clinical Category C or B–see Table B in Appendix C: Supplemental Information)[38] are at high risk of disease progression and death. The Panel recommends treatment for all such children, regardless of immunologic or virologic status. However, children aged ≥1 year who have mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than children with more severe clinical symptoms.[39] It should also be noted that some Clinical Category B conditions, such as a single episode of serious bacterial infection, may be less prognostic of the risk of disease progression. Consideration of CD4 cell count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, the strength of recommendations to initiate cART in asymptomatic individuals is based primarily on risk of disease progression, as determined by baseline CD4 cell count.[9] In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 cell counts <350 cells/mm^3. In HIV-infected adults in Haiti, a randomized clinical trial found significant reductions in mortality and morbidity with initiation of treatment when CD4 cell counts fell to <350 cells/mm^3, compared with deferring treatment until CD4 cell counts fell to <200 cells/mm^3.[10] In observational data in adults, a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting treatment between 1995 and 2003, the risk of AIDS or death was significantly less in adults who started treatment with CD4 cell counts of 200 to 350 cells/mm^3 compared with those who started therapy at CD4 cell counts <200 cells/mm^3.[40]

The Cochrane Collaboration[41] recently published a review on the effectiveness of cART in HIV-infected children aged <2 years based on data from published randomized trials of early versus deferred cART.[17,42] The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that data supporting universal initiation of treatment between ages 1 and 2 years are less compelling.

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 cART in children aged >1 year.[43] This multicenter, open-label trial randomized 300 HIV-infected children aged >1 year (median 6.4 years) to immediate initiation of cART or deferral until the CD4 percentage was <15%. The median baseline CD4 percentage was 19% (IQR 16-22%) and 46% of children in the deferred group started cART 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% (93.7–99.3) in the immediate therapy group (P = 0.6), and immediate cART did not significantly improve neurodevelopmental outcomes.[44] 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 cART. The limited enrollment of children aged <3 years poses restrictions on its value for recommendations in that age group.

No randomized trial data exist to address the comparative efficacy of starting versus deferring treatment at higher CD4 thresholds in HIV-infected adults or children. Two observational studies in adults—the ART Cohort Collaboration (ART-CC) and North American AIDS Cohort Collaboration on Research and Design (NA-

ACCORD)—suggest a higher rate of progression to AIDS or death in patients deferring treatment until the CD4 count is <350 cells/mm^3 compared with patients starting cART at CD4 cell counts of 351 to 500 cells/mm^3.[11,12] The NA-ACCORD study demonstrated a benefit of starting treatment at CD4 cell counts >500 cell/mm^3 compared with starting cART at CD4 cell counts below this threshold;[11] however, the ART-CC cohort found no additional benefit for patients starting cART with CD4 cell counts >450 cells/mm^3.[12] In a third observational study of 5,162 patients with CD4 cell counts between 500 and 799 cells/mm^3, patients who started cART immediately did not experience a significant reduction in progression to AIDS or death (HR: 1.10, 95% CI: 0.67 to 1.79) or death alone (HR: 1.02, 95% CI: 0.49 to 2.12), compared with those who deferred therapy.[14] There are no similar observational data analyses for HIV-infected children.

In children, the prognostic significance of a specific CD4 percentage or count varies with age.[20,45] 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 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).[20,46] 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 of age. 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 and percentages were frequently discordant around established World Health Organization (WHO) and the Pediatric European Network for Treatment of AIDS (PENTA) thresholds for initiation of cART (14% and 21%, respectively).[47] Furthermore, CD4 cell counts were found to provide greater prognostic value over CD4 percentage for short-term disease progression for children aged <5 years as well as in older children. 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. Therefore, the updated pediatric guidelines include CD4 cell count thresholds (which differ for children aged 1 to <3, 3 to 5, and ≥5 years due to age-related changes in absolute CD4 cell count) as well as CD4 percentage thresholds for all children aged >12 months. In the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.

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.[45] Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality[48-50] and lower neurocognitive performance;[51] similar findings have been reported in adults.[52-54] 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).[45] For example, the estimated 1-year risk of death was 2 to 3 times higher in children with plasma HIV RNA of 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. Therefore, the Panel recommends that children of all ages with HIV RNA levels >100,000 copies/mL initiate cART.

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.[32,55-59] In a study of 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.[60] Younger age at initiation of therapy has also been associated with improved immune response and with more rapid growth reconstitution.[25,32,55,60,61] In addition, the PREDICT Study demonstrated improved height z-scores in the early treatment arm compared with no improvement in the deferred arm.[43] Given that disease progression in children aged ≥5 years is similar to that in adults,[46] and observational data in adults show decreased risk of mortality with initiation of therapy when CD4 cell count is <500 cells/mm^3,[11,12] most experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. However, there are no conclusive pediatric data to address the optimal CD4 cell count threshold for initiation of therapy in older children; additional research studies are needed to answer this question in children more definitively. The HHS Adult Treatment Guidelines Panel has moved to endorse initiating cART in all HIV-infected adults regardless of CD4 cell count, using varying strengths of evidence to support different CD4 cell count thresholds[9] and incorporating compelling data demonstrating that cART 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. Comparative studies on the impact of treatment versus treatment delay at specific higher CD4 cell counts have not been performed in children, and observational adult studies have produced conflicting results.[11,12,15] Drug choices are more limited in children than in adults and adequate data to address the potential long-term toxicities of prolonged cART in a developing child 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 cART.[62-64] Medication adherence is the core requirement for successful virologic control, but enforcing consistent adherence in childhood is often challenging.[65] Incomplete adherence leads to the selection of viral resistance mutations but forced administration of ARVs to children may result in treatment aversion or fatigue, which occurs among many perinatally infected children during adolescence.[66] The relative benefits of initiating cART in asymptomatic children with low viral burdens and high CD4 cell counts must be weighed against these potential risks.

The Panel recommends that cART should be initiated in all children who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B condition: single episode of serious bacterial infection [*Table 4* in Goals of Antiretroviral Treatment]), regardless of CD4 percentage/count or HIV RNA level. The Panel also recommends that children of all ages with HIV RNA levels >100,000 copies/mL initiate cART regardless of CD4 count or symptoms.

The Panel also generally recommends treatment for all children aged ≥1 year with no or mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of bacterial infection [*Table 4* in Goals of Antiretroviral Treatment]), with the strength of recommendation differing based on age and CD4 count/percentage. 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. Note that the Panel's recommendations which permit optional deferral of therapy for healthy children >1 year of age are different from the 2013 WHO guidelines, which recommend initiation of therapy for all children <5 years of age, reflecting different approaches in resource-limited settings.

Treatment is strongly recommended regardless of HIV RNA level for children aged 1 to <3 years with CD4 cell counts <1000/mm^3 **or** percentage <25%, and for children aged 3 to <5 years with CD4 cell counts <750 cells/mm^3 **or** percentage <25%, based on observational pediatric data.[20] Treatment should also be considered for children aged 1 to <3 years with CD4 cell counts ≥1000/mm^3 and percentage ≥25% and for children aged 3 to <5 years with CD4 cell counts ≥750 cells/mm^3 and percentage ≥25%, although the strength of the recommendation is lower because of limited data.

For children aged ≥5 years with no or minimal symptoms, treatment is recommended if CD4 cell counts are ≤500 cells/mm^3, regardless of HIV RNA level. The evidence for this recommendation is strongest for children with CD4 cell counts <350 cells/mm^3. For children with CD4 cell counts 350 to 500 cells/mm^3, the recommendation is based on observational data in adults and hence the evidence base is not as strong; this recommendation should not prohibit research studies in children designed to answer this question more definitively. Treatment should also be considered for children who are asymptomatic or have mild symptoms with CD4 counts >500 cells/mm^3, although the strength of the recommendation is lower because of limited data.

In general, except in infants and children with advanced HIV infection, cART does not need to be started immediately. Before initiating therapy, it is important to take time to educate caregivers (and older children) 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 and the higher CD4 cell count threshold now recommended for initiating therapy.

If therapy is deferred, the health care provider should closely monitor a child's virologic, immunologic, and clinical status (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 (e.g., HIV RNA levels approaching 100,000 copies/mL);
- CD4 count or percentage values approaching the age-related threshold for treatment;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

Table 5. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children (page 1 of 2)

Table 5 provides general guidance rather than absolute recommendations for individual patients. Factors to be considered in decisions about initiation of therapy include risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with a child (if age appropriate) and the caregiver. 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.[a]

Age	Criteria	Recommendation
<12 Months	Regardless of clinical symptoms, immune status, or viral load	Treat (**AI** for <12 weeks of age; **AII** for ≥12 weeks)
1 to <3 Years	AIDS or significant HIV-related symptoms[b]	Treat **(AI*)**
	CD4 cell count <1000 cells/mm^3 **or** CD4 percentage <25%,[e]	Treat **(AII)**
	Asymptomatic or mild symptoms[c] **and** CD4 cell count ≥1000 cells/mm^3 or percentage ≥25%	Consider Treatment[d] **(BIII)**
3 to <5 Years	AIDS or significant HIV-related symptoms[b]	Treat **(AI*)**
	CD4 cell count <750 cells/mm^3 or CD4 percentage <25%,[e]	Treat **(AII)**
	Asymptomatic or mild symptoms[c] **and** CD4 cell count ≥750 cells/mm^3 or percentage ≥25%	Consider Treatment[d] **(BIII)**
≥5 Years	AIDS or significant HIV-related symptoms[b]	Treat **(AI*)**
	CD4 cell count ≤500 cells/mm^3,[e]	Treat (**AI*** for CD4 cell count <350 cells/mm^3 and **BII*** for CD4 cell count 350–500 cells/mm^3)
	Asymptomatic or mild symptoms[c] **and** CD4 cell count >500 cells/mm^3	Consider Treatment **(BIII)**
All Ages	HIV RNA levels >100,000 copies/mL[d]	Treat **(AII)**

Table 5. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children (page 2 of 2)

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

Rating of Evidence: I = data from randomized controlled trials in children; I*=data from randomized trials in adults with accompanying data in children from nonrandomized trials or observational cohort studies with long-term clinical outcomes; II: data from well-designed nonrandomized trials or observational cohort studies in children with long-term clinical outcomes; II*= data from well-designed nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in chidren from smaller non-randomized trials or cohort studies with clinical outcomes data; III=expert opinion

[a] Children in whom cART is deferred need close follow-up. Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- CD4 cell count or percentage values approaching the age-related threshold for treatment;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

[b] CDC Clinical Categories B and C (except for the following Category B condition: single episode of serious bacterial infection)

[c] CDC Clinical Category A or N or the following Category B condition: single episode of serious bacterial infection

[d] To avoid overinterpretation of temporary blips in viral load (which can occur during intercurrent illnesses, for example), plasma HIV RNA level >100,000 copies/mL should be confirmed by a second level before initiating cART.

[e] Laboratory data should be confirmed with a second test to meet the treatment criteria before initiation of cART.

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What to Start (Last updated February 12, 2014; last reviewed February 12, 2014)

Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children

Panel's Recommendations

- The Panel recommends initiating combination antiretroviral therapy (cART) in treatment-naive children using one of the following preferred agents plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone combination:
  - For neonates/infants aged ≥42 weeks postmenstrual **and** ≥14 days postnatal to children <3 years: ritonavir-boosted lopinavir **(AI)**;
  - For children aged 3 years to <6 years: efavirenz or ritonavir-boosted lopinavir **(AI*)**;
  - For children aged ≥6 years: ritonavir-boosted atazanavir or efavirenz or ritonavir-boosted lopinavir **(AI*)**.
- The Panel recommends the following preferred dual-NRTI backbone combinations:
  - For children of any age: zidovudine plus (lamivudine or emtricitabine) **(AI*)**;
  - For children aged ≥3 months: abacavir plus (lamivudine or emtricitabine) **(AI)** or zidovudine plus (lamivudine or emtricitabine) **(AI*)**;
    - HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 **(AII*)**;
  - For adolescents at Tanner Stage 4 or 5: abacavir plus (lamivudine or emtricitabine) **(AI)** or tenofovir disoproxil fumarate (tenofovir) plus (lamivudine or emtricitabine) **(AI*)** or zidovudine plus (lamivudine or emtricitabine) **(AI*)**.
- Table 6 provides a list of Panel-recommended alternative and acceptable regimens.
- 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 children aged <42 weeks postmenstrual or <14 days postnatal, data are currently inadequate to provide recommended dosing to allow the formulation of an effective, complete cART regimen (see Special Considerations section).
- Alternative regimens may be preferable for some patients based on their individual characteristics and needs.
- Both emtricitabine and lamivudine, and tenofovir have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection the reader should access the Pediatric Opportunistic Infections Guidelines.

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 recommendations are based on reviews of pediatric and adult clinical trial data published in peer-reviewed journals (the Panel may also review 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 combination antiretroviral therapy (cART) 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 studies in adults, 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 and number of pills;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

The Panel classifies recommended drugs or drug combinations into one of several categories as follows:

- *Preferred:* Drugs or drug combinations are designated as *preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies demonstrate that safety and efficacy are suggested using surrogate markers; 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

A cART regimen for children should generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one active drug from the following classes: non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI), generally boosted with low-dose ritonavir. Although integrase strand transfer inhibitors (INSTIs) or CCR5 antagonists may be considered for first-line treatment of adults, there are insufficient data to recommend these agents as preferred agents for initial therapy in children at this time. 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 7. In addition, because cART 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.

Choice of NNRTI- Versus PI-Based Initial Regimens

Preferred regimens for initial therapy include both NNRTI- and protease inhibitor (PI)-based regimens. The selection of a NNRTI- or PI-based regimen should be based on patient characteristics, especially age, and preferences, results of viral drug resistance testing, and information cited below.

Recent clinical trial data in children provide some guidance for choosing between a NNRTI-based regimen and a PI-based regimen for initial therapy. The P1060 study compared a nevirapine-based regimen to a lopinavir-based regimen in HIV-infected infants and children aged 2 months to 35 months in 6 African countries and India. Infants and children in this study were stratified at entry based on prior maternal or infant exposure to peripartum single-dose nevirapine prophylaxis or no exposure, and randomized to receive either zidovudine, lamivudine, and nevirapine or zidovudine, lamivudine, and ritonavir-boosted lopinavir (lopinavir boosted with low-dose ritonavir). Median age was 0.7 years in the single-dose nevirapine-exposed and 1.7 years in the nevirapine-unexposed children. Among infants and children with prior exposure to nevirapine, 39.6% of children in the nevirapine group reached a study endpoint of death, virologic failure, or toxicity by Week 24 compared with 21.7% of children in the ritonavir-boosted lopinavir group.[1] Among infants and children with no prior nevirapine exposure, 40.1% of children treated with nevirapine met a study endpoint after 24 weeks in the study compared with 18.4% of children who received ritonavir-boosted lopinavir.[2] Based on these data, a PI-based regimen containing ritonavir-boosted lopinavir is the preferred initial regimen for HIV-infected children aged <3 years.

A comparison of a PI-based regimen and a NNRTI-based regimen was also undertaken in HIV-infected treatment-naive children aged 30 days to <18 years in PENPACT-1 (PENTA 9/PACTG 390) (the study did not dictate the specific NNRTI or PI drug initiated). In the PI-based group, 49% of children received ritonavir-boosted lopinavir and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. Efavirenz was recommended only for children aged >3 years. 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 cART regimen. In both groups, 82% of children had viral loads <400 copies/mL, suggesting that selection of a NNRTI or a PI did not influence outcome. Although the age of participants overlapped somewhat between P1060 and PENPACT-1 (in PENPACT-1, the lowest quartile was aged <2.8 years), PENPACT-1 generally enrolled older children.[3]

Recent data from PROMOTE-pediatrics trial also demonstrated comparable virologic efficacy among children randomized to receive either a NNRTI or ritonavir-boosted lopinavir-based cART.[4] Children were aged 2 months to <6 years, with a median of 3.1 years (intermediate between P1060 and PENPACT 1). Children had no perinatal exposure to nevirapine and could be cART-naive or currently receiving cART with HIV RNA level <400 copies/mL at enrollment. In the NNRTI arm, children <3 years of age received nevirapine and those aged >3 years primarily received efavirenz. Among 185 children randomized to ritonavir-boosted lopinavir- (n = 92) or NNRTI- (n = 93) based cART, the proportion with HIV RNA level <400 copies/mL at 48 weeks was 80% in the ritonavir-boosted lopinavir arm versus 76% in the NNRTI-arm, a difference of 3.8% (95% CI: -8.9% to +17).

With regard to virologic suppression, the results of the P1060 study suggest that a PI-based regimen containing ritonavir-boosted lopinavir should be the preferred initial regimen for children aged <3 years. However, in both single-dose nevirapine-exposed and -unexposed children in the P1060 study, participants receiving the nevirapine-based regimen demonstrated better immunologic response and growth than those receiving a ritonavir-boosted lopinavir-based regimen, although these differences did not achieve statistical significance. Similarly, in the NEVEREST study, children switched to a nevirapine regimen showed better immune and growth responses than those continuing a ritonavir-boosted lopinavir regimen.[5] Based on these findings, the potential for improved lipid profiles with nevirapine use,[5,6] and the poor palatability of liquid ritonavir-boosted lopinavir, liquid nevirapine remains an acceptable alternative for infants who were not exposed to peripartum single-dose nevirapine or infant nevirapine prophylaxis and who cannot tolerate ritonavir-boosted lopinavir. In children aged ≥3 years, either a NNRTI-based or a PI-based regimen is acceptable.

NNRTI-Based Regimens (One NNRTI + Two-NRTI Backbone)

Summary: NNRTI-Based Regimens

Efavirenz (aged ≥3 months), etravirine (aged ≥6 years) and nevirapine (aged ≥15 days) have an FDA-approved pediatric indication for treatment of HIV infection. In the United States, nevirapine is the only NNRTI available in a liquid formulation. Efavirenz capsules can be opened and sprinkled on age-appropriate food. This administration procedure has recently been approved by the FDA for use in children as young as age 3 months who weigh at least 3.5 kg. However, at this time, there are concerns regarding variable PK of the drug in the very young and the committee does not endorse its use for infants and children aged 3 months to 3 years at this time. Additional data about the PK in children in this age group are awaited. Advantages and disadvantages of different NNRTI drugs are delineated in Table 7. Use of NNRTIs as initial therapy preserves the PI class for future use and confers lower risk of dyslipidemia and fat maldistribution than use of some agents in the PI class. In addition, for children taking solid formulations, NNRTI-based regimens generally have a lower pill burden than PI-based regimens. The major disadvantages of the current NNRTI drugs FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance, 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. Like PIs, 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.

Efavirenz, in combination with 2 NRTIs, is the preferred NNRTI for initial therapy of children aged ≥3 years based on clinical trial experience in adults and children. Nevirapine is considered as a component of an alternative NNRTI-based regimen because of its association with the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare but potentially life-threatening hepatitis,[7,8] and conflicting data about virologic efficacy compared to preferred regimens.

Currently, there are insufficient data to recommend etravirine or rilpivirine-based regimens as initial therapy in children. Etravirine is currently FDA-approved only for treatment-experienced adults and it is unlikely that it will be investigated in treatment-naive children.

Preferred NNRTI

Efavirenz as Preferred NNRTI (For Children Aged ≥3 Years) (AI*)
In clinical trials in HIV-infected adults, 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 ritonavir-boosted lopinavir, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.[9-16]

Efavirenz in combination with two NRTIs or with a NRTI and a PI has been studied in HIV-infected children[17-23] with results comparable to those seen in adults. For children aged ≥3 years who are unable to swallow pills, efavirenz capsules can be opened and sprinkled on age-appropriate food. Bioequivalence data based on bioavailability and PK support this option.[24]

The major limitations of efavirenz are central nervous system (CNS) side effects in both children and adults; reported adverse effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after initiating efavirenz. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the occurrence was more frequent in adults with higher levels of drug.[25-28] In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than adults.[21,23] In addition, first-trimester exposure to efavirenz is potentially teratogenic (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Although emerging information about the use of efavirenz in pregnancy is reassuring,[29-31] 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).**

Alternative NNRTI

Nevirapine as Alternative NNRTI (AI)

Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).[32] Nevirapine in combination with two NRTIs or with a NRTI and a PI has been studied in HIV-infected children.[33-35]

Randomized clinical trials in adults have not demonstrated virologic inferiority for a nevirapine-based regimen compared to either efavirenz or atazanavir-based regimens. In the 2NN trial, virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine vs. 62% of those receiving efavirenz).[36] Similarly, in the ARTEN trial, cART - naive participants were randomized to nevirapine 200 mg twice daily, nevirapine 400 mg once daily, or ritonavir-boosted atazanavir all in combination with tenofovir disoproxil fumarate (tenofovir)/emtricitabine. By 48 weeks, similar proportions of subjects in each group had at least 2 consecutive plasma HIV RNA levels <50 copies/mL (66.8% for nevirapine vs. 65.3% for atazanavir/ritonavir).[37]

In the P1060 trial of children aged <3 years, a nevirapine-based regimen was less effective compared to a ritonavir-boosted lopinavir regimen, regardless of prior history of maternal nevirapine exposure.[1,2] In PENPACT-1 and PROMOTE-pediatrics, there was no difference in virologic suppression between NNRTI-based and PI-based regimens (see Choice of NNRTI- Versus PI- Based Initial Regimens). However, interpretation of these studies is complicated by the fact that the children in P1060 were younger than those in PROMOTE-pediatrics and PENPACT-1. Furthermore efavirenz was allowed in PROMOTE-pediatrics and PENPACT-1 and was preferentially prescribed to older children. In addition, in the PROMOTE-pediatrics study, both ARV-naive and experienced but virologically suppressed children were enrolled. Comparisons of a nevirapine-based regimen and an efavirenz-based regimen in children in non-randomized studies have suggested that efavirenz is more effective. An analysis of children and adults starting first-line cART in Uganda demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years).[38] Few had been exposed to peripartum nevirapine. In addition, a recent report of 804 children aged 3 to 16 years who received either efavirenz (n = 421) or nevirapine (n = 383) in the Botswana national treatment program demonstrated increased rates of virologic failure (including both failure to suppress and rebound) among those receiving nevirapine (OR = 2.0, 95% CI 1.4–2.7). Time to virologic failure also favored an efavirenz regimen.[39]

In addition to concerns about virologic efficacy, adult randomized clinical trials have demonstrated higher rates of toxicity and drug discontinuation in the nevirapine arms. In the 2NN study, serious hepatic toxicity was more frequent in the nevirapine arm than in the efavirenz arm (hepatic laboratory toxicity in 8%−14% of those on nevirapine, compared with 5% on efavirenz).[36] In the ARTEN trial, more participants in the nevirapine arms discontinued study drugs because of adverse events (13.6% vs. 2.6%, respectively) or lack of efficacy (8.4% vs. 1.6%, respectively).[37] Data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 cell counts and in women, particularly women with CD4 cell counts >250 cells/mm^3 and men with CD4 cell counts >400 cells/mm^3. In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults.[34,35,40,41] Although there is limited evidence in children of hepatic toxicity associated with CD4 count, overall toxicity has been reported to be more frequent among children with CD4 percentage ≥15% at therapy initiation.[42] 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 this substitution should be attempted with caution.[43]

Because of the greater potential for toxicity and possibly increased risk of virologic failure, nevirapine-based regimens are considered an alternative rather than the preferred NNRTI in children aged ≥3 years. In children aged <3 years, nevirapine is considered an alternative because of increased risk of virologic failure compared to a PI ritonavir-boosted lopinavir regimen.

Nevirapine should not be used in postpubertal adolescent girls with CD4 cell counts >250/mm^3 because of the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk.[8] Nevirapine also should be used with caution in children with elevated pretreatment liver function tests.

PI-Based Regimens (PIs [Boosted or Unboosted] Plus Two-NRTI Backbone)

Summary: PI-Based Regimens

Nine PIs are currently FDA-approved for use in adults and seven are approved for use in children. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. 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 7 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 coadministered with some PIs, increasing drug exposure by prolonging the half-life of the boosted PI. Currently only ritonavir-boosted lopinavir 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 low-dose ritonavir increases the potential for hyperlipidemia[44] and drug-drug interactions.

The Panel recommends either atazanavir with low-dose ritonavir or coformulated ritonavir-boosted lopinavir as the preferred PI for initial therapy in children based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, availability of appropriate dosing information, and experience as initial therapy in both resource-rich and resource-limited areas. Ritonavir-boosted darunavir is considered an alternative PI regimen. Several regimens including unboosted atazanavir in adolescents aged ≥13 years, ritonavir-boosted fosamprenavir in children aged ≥6 months, and nelfinavir are considered appropriate for use in special circumstances when preferred and alternative drugs are not available or are not tolerated.

Preferred PIs

Atazanavir with Low-Dose Ritonavir as Preferred PI (for Children ≥6 Years) (AI*)
Atazanavir is a once-daily PI that was FDA-approved in March 2008 for use in children aged ≥6 years. It has efficacy equivalent to efavirenz-based and ritonavir-boosted-lopinavir-based combination therapy when given in combination with 2 NRTIs in treatment-naive adults.[9,45-47] Seventy-three percent of 48 treatment-naive South African children achieved viral load <400 copies/mL by 48 weeks when given atazanavir with or without low-dose ritonavir in combination with 2 NRTIs.[48] Among 43 treatment-naive children aged 6 to18 years in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 51% and 47% achieved viral load <400 copies/mL and <50 copies/mL, respectively, by 96 weeks.[49,50] When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children aged ≥6 years[51-53] and in ARV-naive adults appears to be associated with fewer PI-resistance mutations at virologic failure compared with atazanavir given without ritonavir boosting.[54] The main adverse effect associated with ritonavir-boosted atazanavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher with low-dose ritonavir boosting than with atazanavir alone.[44]

Lopinavir with Low-Dose Ritonavir as Preferred PI (for Infants with a Postmenstrual Aged ≥42 Weeks and Postnatal Age ≥14 Days) (AI)

In clinical trials of treatment-naive adults, regimens containing ritonavir-boosted lopinavir plus 2 NRTIs have been demonstrated to be comparable to a variety of other regimens including atazanavir, darunavir (at 48 weeks), fosamprenavir, ritonavir-boosted saquinavir, and efavirenz. Ritonavir-boosted lopinavir was demonstrated to have superior virologic activity when compared to nelfinavir.[11,45,47,55-60] Ritonavir-boosted lopinavir has been studied in both ARV-naive and -experienced children and has demonstrated durable virologic activity and low toxicity (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).[1,61-67] In addition, dosing and efficacy data in infants as young as age 25 days are available.[64,68] Post-marketing reports of ritonavir-boosted lopinavir-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 ritonavir-boosted lopinavir 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. In addition, although once-daily ritonavir-boosted lopinavir is FDA-approved for initial therapy in adults,[69] PK data in children do not support a recommendation for once-daily dosing in children.[70,71]

Alternative PI

Darunavir with Low-Dose Ritonavir Administered Once Daily as Alternative PI (For Children Aged ≥12 Years) or Twice Daily (For Children Aged ≥3 to 12 Years) (AI*)

Darunavir combined with low-dose ritonavir is FDA-approved for ARV-naive and -experienced adults and for ARV-naive and -experienced children aged ≥3 years. In a randomized, open-label trial in adults, darunavir/ritonavir (800/100 mg once daily) was found to be non-inferior to ritonavir-boosted lopinavir (once or twice daily) when both boosted PIs were administered in combination with tenofovir/emtricitabine. Adverse events were also less common in the darunavir/ritonavir group (P <0.01).[55,72] Unfortunately, there is limited information about the use of darunavir combined with low-dose ritonavir as part of an initial therapy regimen for HIV-infected children. To date the only clinical trial of darunavir with low-dose ritonavir as initial therapy is a study of once-daily ritonavir-boosted darunavir 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.[73,74]

Data in treatment-experienced children have also demonstrated that the regimen is effective and well-tolerated. In a study of treatment-experienced children (aged 6–17 years), DELPHI, twice-daily ritonavir-boosted-darunavir-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks.[75] In another study of treatment-experienced pediatric subjects (aged 3 to <6 years and weight ≥10 kg to <20 kg), ARIEL, 57% of subjects had HIV-1 RNA <50 copies/mL and 81% were less than 400 copies/mL after 24 weeks of treatment.[76] Twenty children completed the trial; 1 stopped prematurely because of vomiting. Based on data from these studies and the findings of high potency and low toxicity in adults, ritonavir-boosted darunavir is recommend as an alternative agent for initial therapy in HIV-infected children. Some experts, however, would only recommend ritonavir-boosted darunavir for treatment-experienced children and reserve its use for patients with resistant mutations to other PIs.

As noted above, ritonavir-boosted darunavir is approved for once-daily use in adults and children. In addition to the DELPHI study noted above, a PK study of 24 patients, aged 14 to 23 years, receiving once-daily darunavir demonstrated darunavir exposure similar to that in adults receiving once-daily therapy although there was a trend toward lower exposures in those aged <18 years.[77] Also, 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 area under the curve (AUC) 24- hour equivalent to 128% of the adult AUC 24 hour.[78] Based on these findings, the FDA has approved use of once-daily darunavir in children. At this time, the Panel recommends that once-daily dosing of ritonavir-boosted darunavir as alternative initial therapy be considered only in treatment-naive adolescents aged >12 years. Additional experience with once-daily dosing of ritonavir-boosted darunavir in children aged ≥3 years through age 12 years is awaited. Also, if darunavir resistance-associated substitutions are present (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V), once-daily administration should not be used. If ritonavir-boosted darunavir is used as alternative therapy in children aged <12 years or if any of these resistance-associated substitutions are present, the Panel recommends twice-daily dosing.

PIs for Use in Special Circumstances

Atazanavir without Ritonavir Boosting in Children Aged ≥13 Years (BII*)
Although unboosted atazanavir is 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[53] (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information on dosing used in IMPAACT/PACTG P1020A). If using unboosted atazanavir in treatment-naive patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because this combination demonstrated inferior virologic response in adults in ACTG 5175.[79] Also, unboosted atazanavir should not be used in combination with tenofovir because concomitant administration results in lower atazanavir exposure. If didanosine, emtricitabine, **and** atazanavir are used in combination, patients should be instructed to take didanosine and atazanavir at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach. The complexity of this regimen argues against its use.

Fosamprenavir with Low-Dose Ritonavir as Alternative PI (for Children Aged ≥6 Months) (AI*)
Fosamprenavir (the prodrug of amprenavir) is available in a pediatric liquid formulation and a tablet formulation. In an adult clinical trial, fosamprenavir with low-dose ritonavir was demonstrated to be noninferior to ritonavir-boosted lopinavir.[57] In June 2007, fosamprenavir suspension was FDA-approved for use in pediatric patients aged ≥2 years. The approval was based on 2 open-label studies in pediatric patients aged 2 to18 years.[80,81] PK, safety and efficacy were assessed in an international study of PI- naive and -experienced pediatric patients, aged 4 weeks to 2 years[82] Overall, fosamprenavir was well tolerated except for vomiting and effective in suppressing viral load and increasing CD4 cell count (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). These data supported FDA approval for use in PI-naive children as young as 4 weeks who were born at ≥38 weeks' gestation and had attained a postnatal age of 28 days. Young infants, however, demonstrated low drug exposure. Fosamprenavir should always be used in combination with low-dose ritonavir boosting and only for children aged ≥6 months. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

Nelfinavir for Children Aged ≥2 Years (BI*)
Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children aged ≥2 years in special circumstances. The pediatric experience with nelfinavir-based regimens in ARV-naive and -experienced children is extensive, with follow-up in children receiving the regimen for as long as 7 years.[83] The drug has been well tolerated—diarrhea is the primary adverse effect; however, in clinical studies the virologic potency of nelfinavir has varied greatly, with reported rates of virologic suppression ranging from 26% to 69% (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naive pediatric patients.[84] In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus 80% of children with therapeutic nelfinavir troughs (>0.8 mg/L).[84] The interpatient variability in plasma concentrations is great in children, with lower levels in younger children.[85-90] The optimal dose of nelfinavir in younger children, particularly in those aged <2 years, has not been well defined. These data, combined with data in adults showing inferior potency of nelfinavir compared with other PIs and efavirenz, balanced against the advantage of a PI that is not coadministered with low-dose ritonavir for boosting,[60,91-94] make nelfinavir an agent for use in special

circumstances in treatment-naive children aged ≥2 years and not recommended for treatment of children aged <2 years.

Nelfinavir is currently available only as tablets, which can be dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable PK parameters in a study in adults.[95]

Integrase Strand Transfer Inhibitor (INSTI)-Based Regimens (INSTIs Plus Two-NRTI Backbone)

Summary: INSTI-Based Regimens

INSTIs for Use in Special Circumstances

Dolutegravir has recently been approved by the FDA for use in children aged 12 years and greater and weighing at least 40 kg. The approval was supported by data from a study of 23 treatment experienced but INSTI-naive children and adolescents.[96] The drug has a very favorable safety profile and can be dosed once daily in treatment of INSTI-naive patients.

Raltegravir is FDA-approved for treatment of HIV-1-infected children aged ≥2 years and weight ≥10 kg. It is available in film-coated tablets and chewable tablets. However, these two formulations are not bio-equivalent, thus they require different dosing and are not interchangeable. Oral granules for suspension are currently under investigation. Safety and efficacy data are promising, but at this time, there are no data on raltegravir use as initial therapy in HIV-infected children. However, because of its favorable safety profile, lack of significant drug interactions, and palatability, raltegravir may be considered as initial therapy in special circumstances.[97,98]

Selection of Dual-NRTI Backbone as Part of Initial Combination Therapy

Summary: Selection of Dual-NRTI Backbone Regimen

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, 7 NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, and tenofovir) 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 tenofovir in combination with lamivudine or emtricitabine.[19,51,83,89,99-107] Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 7.

In the dual-NRTI regimens listed below, lamivudine and emtricitabine are interchangeable. Both lamivudine and emtricitabine are well tolerated with few adverse effects. 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 tenofovir or zidovudine). The main advantage of emtricitabine over lamivudine is that it can be administered once daily. 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 tenofovir based on decreased viral fitness.[108,109]

Preferred Dual-NRTI Regimens (in Alphabetical Order)

Abacavir in Combination with Lamivudine or Emtricitabine (for Children ≥ 3 Months) (AI)

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.[110,111] In 5 years of follow-up, abacavir plus lamivudine maintained significantly better viral suppression and growth in children than did zidovudine plus lamivudine and zidovudine plus abacavir.[111] However, abacavir/lamivudine or emtricitabine has the potential for abacavir-associated life-threatening HSRs in a small proportion of patients. Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see Appendix A: Pediatric Antiretroviral Drug Information); however, in the United States, the prevalence of HLA-B*5701 is much lower in African Americans and Hispanics (2%–2.5%) than in whites (8%).[112] Prevalence in Thai and Cambodian children is approximately 4%.[113] Pretreatment screening for HLA-B*5701 before initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir HSRs in HIV-infected adults (from 7.8% to 3.4%).[114] Before initiating 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*)**.

An advantage of an abacavir regimen is the potential to switch to once-daily dosing in children with undetectable plasma RNA after approximately 24 weeks of therapy. Three small studies have now demonstrated equivalent drug exposure following a change from a twice-daily to a once-daily dosing regimen in children aged ≥3 months who had undetectable or low, stable plasma RNA after a variable period of twice-daily abacavir dosing. Two of the three demonstrated continued virologic suppression and one did not assess viral suppression.[115-118] Recently, the ARROW trial reported findings from 669 HIV-infected children who had been receiving abacavir and lamivudine twice daily for 36 weeks and were randomized to either continue twice-daily dosing or change to once-daily dosing. At 48 weeks, once-daily abacavir was non-inferior to twice-daily dosing in terms of viral suppression;[119] therefore, the Panel suggests that in clinically stable patients with undetectable plasma RNA and stable CD4 cell counts for more than 6 months, switching from twice-daily to once-daily dosing of abacavir is recommended as part of a once-daily regimen.

Tenofovir in Combination with Lamivudine or Emtricitabine (for Adolescents, Tanner Stage 4 or 5) (AI*)

Tenofovir is FDA-approved for use in children and adolescents aged ≥2 years. Because of decreases in bone mineral density (BMD) observed in adults and children receiving tenofovir, the Panel has opted to consider use of tenofovir based on Tanner stage. We have reserved our strongest recommendation in support of using tenofovir for adolescents who are in the late stages of or who have completed puberty (Tanner stages 4 and 5). Tenofovir can be used in younger children after weighing potential risks of decreased BMD versus benefits of therapy. In comparative clinical trials in adults, tenofovir when used with lamivudine or emtricitabine as a dual-NRTI backbone was superior to zidovudine used with lamivudine and efavirenz in viral efficacy.[120,121] In ACTG 5202, adults who had a screening HIV-1 RNA ≥100,000 copies/mL receiving tenofovir/emtricitabine as part of a cART regimen had a longer time to virologic failure and to first adverse event compared to those assigned to abacavir/lamivudine.[122] However, this has not been demonstrated in other comparative trials or in a meta-analysis.[123,124] Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an oral sprinkle/granule formulation.[102-105] The use of tenofovir in pediatric patients aged 2 years to <18 years is approved by the FDA based on data from 2 randomized studies. In study 321, 87 treatment-experienced subjects aged 12 to <18 years, were randomized to receive tenofovir or placebo plus optimized background regimen for 48 weeks. Although there was no difference in virologic response between the two groups, the safety and PKs of tenofovir in children in the study were similar to those in adults receiving tenofovir.[106] In study 352, 92 treatment-experienced children, aged 2 years to <18 years with virologic suppression on stavudine- or zidovudine-containing regimens were randomized to either replace stavudine or zidovudine with tenofovir or continue their original regimen. After 48 weeks, 89% of subjects receiving tenofovir and 90% of subjects continuing their original regimen had HIV-1 RNA concentrations <400 copies/mL.[107] Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents Tanner Stage 4 or 5 **(AI*)**. The fixed-dose combination of tenofovir and emtricitabine and the fixed-dose triple combination of tenofovir, emtricitabine, and efavirenz both allow for once-daily dosing, which may help improve adherence in older adolescents.

In some, but not all, studies, decreases in BMD have been observed in both adults and children taking tenofovir for 48 weeks.[102-105,125,126] At this time, data are insufficient to recommend use of tenofovir as part of a preferred regimen for initial therapy in infected children in Tanner Stages 1 through 3, for whom the risk of bone toxicity may be greatest[102,105] (see Appendix A: Pediatric Antiretroviral Drug Information for more detailed pediatric information). It is important to note that although decreases in BMD are observed, the clinical significance of these changes is not yet known. Renal toxicity has been reported in children receiving tenofovir.[127-130] Given the potential for bone and renal toxicity, tenofovir may be more useful for treatment of children in whom other ARV drugs have failed than for initial therapy of treatment-naive younger children. Numerous drug-drug interactions with tenofovir and other ARV drugs, including didanosine, ritonavir-boosted lopinavir, atazanavir, and tipranavir, complicate appropriate dosing of tenofovir.

Both emtrictabive and lamivudine, and tenofovir have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and interactions of ARV drugs with treatment for Hepatitis C and tuberculosis the reader should access the Pediatric Opportunistic Infections Guidelines.

Zidovudine in Combination with Lamivudine or Emtricitabine (AI*)

The most extensive experience in children is with zidovudine in combination with lamivudine. Data on the safety of this combination in children are extensive and the combination is generally well tolerated.[131] The major toxicities associated with zidovudine/lamivudine are bone marrow suppression, manifested as macrocytic anemia and neutropenia and an association with lipoatrophy; minor toxicities include gastrointestinal toxicity and fatigue. In addition, the combination of zidovudine and lamivudine is acceptable in infants less than 3 months of age.

Alternative Dual-NRTI Regimens

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine **(BII)**, didanosine in combination with lamivudine or emtricitabine **(BI*)** and tenofovir in combination with lamivudine or emtricitabine in children and adolescents who are Tanner Stage 3 (as opposed to Tanner Stages 4 and 5, where this is a preferred dual-NRTI regimen) **(BI*)**. There is considerable experience with use of these dual-NRTI regimens in children, and in a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities.[131] However, 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.[89,111] The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naive children aged 3 to 21 years, long-term virologic suppression was achieved with a once-daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy.[19] Prescribing information for didanosine recommends administration on an empty stomach. However, this 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. A comparison of didanosine given with or without food in children found that systemic exposure was similar but with slower and more prolonged absorption with food.[132] To improve adherence, some practitioners recommend administration of didanosine without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferable to administer didanosine under fasting conditions when possible.

Dual-NRTI Regimens for Use in Special Circumstances

The dual-NRTI combinations of stavudine with lamivudine or emtricitabine in children of any age are recommended for use in special circumstances. Stavudine is recommended for use only in special circumstances because the ARV is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs.[133-138] Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than children receiving zidovudine-containing combinations.[131] In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive abacavir or tenofovir, stavudine may be preferable to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

In children aged ≥2 years and those who are prepubertal or in the early stages of puberty (Tanner Stages 1 and 2), tenofovir in combination with lamivudine or emtricitabine is also recommended for use in special circumstances. As discussed above, the use of tenofovir during puberty when bone toxicity may be greatest may require caution. However, tenofovir may be a reasonable choice for initial therapy in children with demonstrated resistance to other NRTIs, coinfection with hepatitis B virus, or in those desiring a once-daily NRTI where abacavir is not an option. The Panel awaits additional safety data, especially with the recently licensed powder formulation, before providing a broader recommendation in younger children.

Both emtricitabine and lamivudine, and tenofovir have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection the reader should access the Pediatric Opportunistic Infections Guidelines.

Special Considerations

Treatment of Premature Infants and Infants Younger than Age 15 days

For infants aged <15 days and for premature infants (until 42 weeks' corrected gestational age) we currently do not have sufficient PK data to allow the formulation of an effective, complete cART regimen.

Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of ARV drugs. Reports of cardiovascular, renal, and CNS toxicity associated with ritonavir-boosted lopinavir in young infants preclude the administration of this agent in the first 2 weeks of life. The IMPAACT network is planning a study of early treatment of infants. Based on PK modeling, an investigational dose of 6 mg/kg of nevirapine administered twice daily to full-term infants will be tested. Providers considering treatment of infants aged < 2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will have to include weighing the risks and benefits of using unapproved ARV drug dosing, and incorporate case-specific factors such as exposure to perinatal ARV prophylaxis.

Table 6. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 1 of 2)

A cART regimen in treatment-naive children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI (generally with low-dose ritonavir boosting) plus a 2-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Table 7).

Preferred Regimens	
Children aged ≥14 days to <3 years[a]	Two NRTIs **plus** LPV/r
Children aged ≥3 years to <6 years	Two NRTIs **plus** EFV[b] Two NRTIs **plus** LPV/r
Children aged ≥6 years	Two NRTIs **plus** ATV **plus** low-dose RTV Two NRTIs **plus** EFV[b] Two NRTIs **plus** LPV/r
Alternative Regimens	
Children aged >14 days	Two NRTIs **plus** NVP[c]
Children aged ≥3 years to <12 years	Two NRTIs **plus** twice-daily DRV **plus** low-dose RTV
Children aged ≥12 years	Two NRTIs **plus** once-daily DRV **plus** low-dose RTV[d]
Regimens for Use in Special Circumstances	
Children aged ≥6 months[e]	Two NRTIs **plus** FPV **plus** low-dose RTV
Children aged ≥2 years	Two NRTIs **plus** NFV Two NRTIs **plus** RAL
Children ≥ 12 years	Two NRTIs **plus** DTG
Treatment-naive adolescents aged ≥13 years and weighing >39 kg	Two NRTIs **plus** ATV unboosted

Table 6. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 2 of 2)

Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children of any age	ZDV **plus** (3TC **or** FTC)
Children aged ≥3 months	ABC **plus** (3TC **or** FTC) ZDV **plus** (3TC **or** FTC)
Adolescents at Tanner Stage 4 or 5	ABC **plus** (3TC **or** FTC) TDF **plus** (3TC **or** FTC) ZDV **plus** (3TC **or** FTC)
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 ≥3 months	ZDV **plus** ABC
Children at Tanner Stage 3 and adolescents	TDF **plus** (3TC **or** FTC)
2-NRTI Regimens for Use in Special Circumstances	
d4T **plus** (3TC or FTC)	
TDF **plus** (3TC or FTC) (prepubertal children aged ≥2 years and adolescents, Tanner Stage 1 or 2)	

[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] EFV should be used only in children aged ≥3 months with weight ≥3.5 kg but is not recommended 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.

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

[d] DRV once daily should not be used if resistance-associated substitutions are present (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V).

[e] FPV with low-dose RTV should only be administered to infants born at ≥38 weeks' gestation who have attained a postnatal age of 28 days and to infants born before 38 weeks' gestation who have reached a postmenstrual age of 42 weeks.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, cART = combination antiretroviral therapy, d4T = stavudine, ddI = didanosine, DRV = darunavir, DTG = dolutegravir, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV/r = fixed-dose formulation ritonavir-boosted lopinavir, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL=raltegravir, RTV = ritonavir, TDF = tenofovir, ZDV = zidovudine

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 1 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs In Alphabetical Order		NNRTI Class Advantages: • Long half-lives. • 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 nevirapine). • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4).
	EFV	• Potent ARV activity. • Once-daily administration. • Can give with food (but avoid high-fat meals). • Capsules can be opened and added to food.	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects). • Rash (generally mild). • No commercially available liquid. • Limited data on dosing for children aged <3 years. • 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. • Generally need to initiate therapy with a lower dose and increase in a stepwise fashion.This is to allow for autoinduction of NVP metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing necessary in children with BSA < 0.58 m^2.
PIs In Alphabetical Order		PI Class Advantages: • NNRTI-sparing. • Clinical, virologic, and immunologic efficacy well documented. • Resistance to PIs requires multiple mutations. • When combined with dual NRTI backbone, targets HIV at 2 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. • Many PIs require low-dose ritonavir boosting resulting in associated drug interactions.

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 2 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	ATV/r	• Once-daily dosing. • 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 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 (see RTV).
	ATV	• Once-daily dosing. • Less effect on TG and total cholesterol levels than other PIs.	• No liquid formulation. • Food effect (should be administered with food). • Indirect hyperbilirubinemia common but asymptomatic. • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG). • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations. • Unboosted ATV cannot be used with TDF.
	DRV/r	• Effective in PI-experienced children when given with low-dose RTV boosting. • Can be used once daily in children aged ≥12 years.	• Pediatric pill burden high with current tablet dose formulations. • No liquid formulation. • 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 (see RTV). • Can only be used once daily in absence of certain PI-associated resistance mutations.
	FPV/r	• Oral prodrug of APV with lower pill burden. • Pediatric formulation available, which should be given to children with food.	• Skin rash. • More limited pediatric experience than preferred PI. • Must be given with food to children. • RTV component associated with large number of drug interactions (see RTV). • Contains sulfa moiety. Potential for cross-sensitivity between FPV and other drugs in sulfonamide class is unknown. • Should only be administered to infants born at ≥38 weeks' gestation and who have attained a postnatal age of 28 days.

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	LPV/r	• Coformulated 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 (see RTV). • 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 pre-existing conduction system defects (can prolong PR and QT interval of ECG).
	NFV	• Can give with food. • Simplified 2-tablet (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate.	• Diarrhea. • Food effect (should be administered with food). • Appropriate dosage for younger children not well defined. • Adolescents may require higher doses than adults. • Less potent than boosted PIs.
INSTI		Integrase Inhibitor Class Advantages: • Susceptibility of HIV to a new class of ARVs.	Integrase Inhibitor Class Disadvantages: • Limited data on pediatric dosing or safety.
	DTG	• Once daily administration. • Can give with food.	• Limited data on pediatric dosing or safety. • Drug interactions with EFV, FPV/r, TPV/r and rifampin necessitating twice daily dosing.
	RAL	• Susceptibility of HIV to a new class of ARVs. • Can give with food. • Available in a chewable tablet.	• Limited data on pediatric dosing or safety. • Potential for rare systemic allergic reaction or hepatitis.
Dual-NRTI Pairs 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.	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
	d4T **plus** (3TC **or** FTC)	• Extensive pediatric experience. • Palatable liquid formulations. • Can give with food. • FTC is available as a palatable liquid formulation administered once daily.	• d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia.

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 4 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Pairs In Alphabetical Order, continued	ddI **plus** (3TC **or** FTC)	• Delayed-release capsules of ddI may allow once-daily dosing in children aged ≥ 6 years, weighing ≥20 kg, and 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 coadministered with FTC or 3TC). • Limited pediatric experience using delayed-release ddI capsules in younger children. • Pancreatitis, neurotoxicity with ddI.
	TDF **plus** (3TC **or** FTC) for adolescents, Tanner Stage 4 or 5	• Resistance slow to develop. • Once-daily dosing for TDF. • Less mitochondrial toxicity than other NRTIs. • Can give with food. • TDF and FTC are coformulated 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, 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 once-daily 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.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, ATV/r=atazanavir/ritonavir, d4T = stavudine, DRV/r=darunavir/ritonavir, ddI = didanosine, EFV=efavirenz, FPV/r=fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = ritonavir-boosted lopinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PK = pharmacokinetic, RAL = raltegravir, TDF = tenofovir, ZDV = zidovudine

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

Many additional antiretroviral agents (ARVs) 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), or pharmacologic antagonism. These drugs and drug combinations are listed in Table 8.

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 in 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 8.

Antiretroviral Drugs and Combinations Not Recommended for Initial Therapy

In addition to the regimens listed below, several ARVs—including unboosted atazanavir in adolescents aged <13 years, nelfinavir and tenofovir disoproxil fumarate (tenofovir) in children aged <2 years, unboosted darunavir, once-daily dosing of lopinavir/ritonavir, and full-dose ritonavir—are not recommended for use as initial therapy.

Enfuvirtide-Based Regimens

Enfuvirtide, a fusion inhibitor, is Food and Drug Administration (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 (i.e., treatment-experienced children on non-suppressive regimens). Enfuvirtide is not recommended as initial therapy because the drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%).

Fosamprenavir without Ritonavir Boosting

Fosamprenavir without ritonavir boosting has been studied in children aged ≥2 years but is not recommended because the volume of fosamprenavir oral suspension necessary to administer in the absence of ritonavir boosting is prohibitive. In addition, low levels of exposure may result in selection of resistance mutations that are associated with darunavir resistance.

Indinavir-Based Regimens

Although adequate virologic and immunologic responses have been observed with indinavir-based regimens in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis have been reported in pediatric patients using indinavir.[1-4] The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults.[1,4] Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy in children.

Regimens Containing Only NRTIs

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 protease inhibitor (PI)-based regimens. These include studies of zidovudine plus abacavir plus lamivudine, stavudine plus didanosine plus lamivudine, stavudine plus lamivudine plus abacavir, didanosine plus stavudine plus abacavir, tenofovir plus abacavir plus lamivudine, and tenofovir plus didanosine plus lamivudine.[5,6] 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.[7,8] 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.[9] 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 in 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.[10]

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). Although efavirenz plus nelfinavir plus one or two NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naive children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options.[11-13]

Regimens Containing Three NRTIs and a NNRTI

Data are currently insufficient to recommend a regimen of three NRTIs plus a NNRTI in young infants. A recent review of 9 cohorts from 13 European countries suggested superior responses to this 4-drug regimen when compared to boosted PI or 3-drug NRTI regimens.[14] There has been speculation that poor tolerance and adherence to a PI-based regimen may account for differences. The ARROW trial conducted in Uganda and Zimbabwe randomized 1,206 children (median age 6 years) to a standard NNRTI-based 3-drug regimen versus 4-drug regimen (3 NRTIs and a NNRTI). After a 36-week induction period, the children on the four-drug regimen were continued on a dual NRTI plus NNRTI or an all NRTI-based regimen. Although early benefits in CD4 T lymphocyte (CD4) improvement and virologic control were observed in the four-drug arm, these benefits were not sustained after de-intensification to the three-NRTI arm.[15] Furthermore, after a median of 3.7 years on therapy, children in the initial 4-drug arm that changed to an all NRTI-based regimen had significantly poorer virologic control.[16] Based on demonstrated benefits of recommended three-drug regimens and lack of additional efficacy data on the four-drug regimen, the Panel does not currently recommend this regimen.

Saquinavir with Low-Dose Ritonavir

A saquinavir/ritonavir-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naive adults.[17] 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 in Combination with Didanosine

The dual-NRTI combination of stavudine/didanosine is not recommended for use as initial therapy because of greater toxicity when used in combination. In small pediatric studies, stavudine/didanosine demonstrated virologic efficacy and was well tolerated.[18-20] However, in studies in adults, stavudine plus didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine plus lamivudine.[21,22] In addition, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy.[23,24]

Tipranavir-Based Regimens

This agent has been studied in treatment-experienced children and adults. Tipranavir is a PI licensed for use in children age ≥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.

***Not* Recommended for *Initial* Therapy for Children Because of Insufficient Data**

A number of ARV drugs and drug regimens are not recommended for initial therapy of ARV-naive children or for specific age groups because of insufficient pediatric data. These include the dual-NRTI backbone combinations abacavir/didanosine, abacavir/tenofovir, and didanosine/tenofovir. In addition, several new agents appear promising for use in adults but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (CCR5 antagonist), elvitegravir (ISTI), and etravirine and rilpivirine (both NNRTIs). Additionally, there are dosing schedules that 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 8.

Darunavir with Low-Dose Ritonavir when Administered Once Daily (for Children Aged ≥3 to 12 Years)

Data are limited on PK of once-daily ritonavir-boosted darunavir in young children. While modeling studies identified a once-daily dosing regimen now approved by the FDA, the Panel is concerned about the lack of efficacy data for persons aged ≥3 to <12 years treated with once-daily ritonavir-boosted darunavir. Therefore once-daily dosing for initial therapy is not recommended in this age group. For children age ≥3 to <12 years, twice-daily darunavir boosted with ritonavir is an alternate PI regimen. For patients who have undetectable viral load on twice-daily therapy with darunavir boosted with ritonavir, practitioners can consider changing to once-daily treatment to enhance ease of use and support adherence.

Dolutegravir for Children Aged <12 Years

Dolutegravir is an integrase strand transfer inhibitor (INSTI) that has recently been approved by the FDA for use in children aged 12 years and older and weighing at least 40 kg. At this time there is no information about its use in children aged <12 years but a clinical trial in treatment-experienced children aged <12 years is under way.

Efavirenz for Children Aged ≥3 Months to 3 Years

Efavirenz is FDA-approved for use in children as young as age 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 under age 3 years at this time (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). However, should efavirenz be considered, CYP2B6 genotyping that predicts efavirenz metabolic rate should be performed, if available. Therapeutic drug monitoring can also be considered.

Elvitegravir-Based Regimens

Elvitegravir is an INSTI only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, and is FDA-approved for use as combination antiretroviral therapy (cART) in HIV-1-infected cART-naive adults. It is not FDA-approved for use in children aged <18 years. There are no data on its use in individuals younger than age 18 years, and it cannot be considered for use as initial therapy for children at this time (see http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf).

Etravirine-Based Regimens

Etravirine is an NNRTI that has been studied in treatment-experienced children 6 years of age and older. It is associated with multiple interactions with other ARVs, including ritonavir-boosted tipranavir, ritonavir-boosted fosamprenavir, ritonavir-boosted atazanavir, 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.

Rilpivirine-Based Regimens

Rilpivirine is currently available both as a single-agent formulation and a once-daily, fixed-dose combination tablet containing emtricitabine and tenofovir. An ongoing study is assessing the safety and efficacy in adolescents aged 12 to 18 years. In adult studies, reduced viral suppression was observed in patients with initial HIV RNA >100,000 copies/mL.

Maraviroc-Based Regimens

Maraviroc is an entry inhibitor that has been used infrequently in children. A dose finding study in children aged 2 to 18 years is currently under way. 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 9. 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 8. ART 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 aged <13 years and/or weight <39 kg	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
Dual NRTI combination of **ABC plus ddI**	Insufficient data to recommend
Dual NRTI combination of **ABC plus TDF**	Insufficient data to recommend
Dual NRTI combination of **d4T plus ddI**	Significant 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
ENF-containing regimens	Insufficient data to recommend Injectable preparation
ETV-based regimens	Insufficient data to recommend
EVG-based regimens	Insufficient data to recommend
FPV without **RTV** boosting	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-containing regimens for children aged <2 years	Appropriate dose not determined
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Insufficient data to recommend

Table 8. ART 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
Full-dose **RTV** or use of **RTV** as the sole PI	GI intolerance Metabolic toxicity
Regimens containing three NRTIs and an NNRTI	Insufficient data to recommend
RPV-based regimens	Insufficient data to recommend
SQV-based regimens	Limited dosing and outcome data burden
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, ATV = atazanavir, d4T=stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETV = etravirine, EVG = elvitegravir, FPV = fosamprenavir, IDV = indinavir, LPV/r = ritonavir-boosted lopinavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide, TDF = tenofovir disoproxil fumarate, RPV = rilpivirine, TPV = tipranavir

Table 9. ART Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children (page 1 of 2)

Regimen/Component	Rationale	Exceptions
ART Regimens Never Recommended for Children		
One ARV drug alone (monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV • 3TC *or* FTC interim “bridging regimen” in special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence
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 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 used as initial therapy in treatment-naive adults.	• No exceptions
ARV Components Never Recommended as Part of an ARV Regimen for Children		
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

Table 9. ART Regimens or Components that Should <u>Never</u> Be Recommended for Treatment of HIV Infection in Children (page 2 of 2)

Regimen/Component	Rationale	Exceptions
ARV Components <u>Never</u> Recommended as Part of an ARV Regimen for Children, continued		
EFV in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured	• Potential for teratogenicity	• When no other ARV option is available and potential benefits outweigh risks
NVP 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 bioavailablity • Inferior virologic activity compared with other PIs	• No exceptions

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, 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, PI = protease inhibitor, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Last updated February 12, 2014; last reviewed February 12, 2014)

Panel's Recommendations
• Combination antiretroviral therapy (cART) regimens must be individually tailored to the adolescent **(AIII)**. • Appropriate dosing of cART for adolescents may be complex, not always predictable, and dependent upon multiple factors, including body mass and composition and pubertal development **(AII)**. • Effective and appropriate methods should be selected to reduce the likelihood of unintended pregnancy and to prevent secondary transmission of HIV to sexual partners **(AI)**. • Providers should be aware of potential interactions between cART and hormonal contraceptives that could lower contraceptive efficacy **(AII*)**. • 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 do not compromise the woman's health **(BIII)**. Adolescent females who require treatment with efavirenz should undergo pregnancy testing before initiation of treatment and receive counseling about potential fetal risk and desirability of avoiding pregnancy while receiving efavirenz-containing regimens **(AIII)**. • 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

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive combination antiretroviral therapy (cART) history.[1] Adolescents with non-perinatally acquired HIV infection generally follow a clinical course similar to that in adults. Because non-perinatally infected adolescents may be at the initial stages of their HIV disease, they may be potential candidates for early intervention and treatment.[2]

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 drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.[3]

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some protease inhibitors [PIs]) are administered to children at higher weight- or 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. With unboosted PI usage, continued use of these pediatric weight- or surface-area-based doses as a child grows during adolescence can result in medication doses that are higher than the usual adult doses. Data suggesting optimal doses for every ARV drug in adolescents are not available. Appendix A: Pediatric Antiretroviral Drug Information includes a discussion of data relevant to adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

HIV-infected adolescents may be sexually active. Reproductive plans including 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)[4] For additional information please see the Perinatal Guidelines—Reproductive Options for HIV-Concordant and Serodiscordant Couples section.[5]

The possibility of an unplanned pregnancy should also be considered when selecting a cART 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 to preclude misinterpretation or lack of adherence by adolescents with unexpressed plans for pregnancy.[6] For additional information please see the Perinatal Guidelines.[5] 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.

Contraceptive-Antiretroviral Drug Interactions

Several PI and non-nucleoside reverse transcriptase inhibitor drugs alter metabolism of oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the Adult and Adolescent Antiretroviral Guidelines) (http://www.hiv-druginteractions.org/).[7-9] These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related adverse effects. Some newer agents, such as integrase inhibitors (specifically raltegravir), appear to have no interaction with estrogen-based contraceptives.[10] Providers should be aware of these drug interactions and consider alternative or additional contraceptive methods for patients receiving cART.

Whether interactions with cART would compromise the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone acetate [DMPA]) is unknown because these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered in women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional adverse effects, and no clinically significant changes in ARV drug levels.[11,12] At this time, concerns about loss of bone mineral density (BMD) with long-term use of DMPA with or without cART (specifically tenofovir)[13] should not preclude use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility. However, more active monitoring of BMD in young women on DMPA may need to be considered.[13] Minimal information exists about drug interactions with use of newer hormonal contraceptive methods (e.g., the patch and vaginal ring).[14] Women with HIV can use all available contraceptive methods, including intrauterine devices (IUD).[4] Adolescents who want to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with cART use during pregnancy (see the Perinatal Guidelines).[5]

HIV-Infected Pregnant Adolescents and Outcomes

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 than for nonpregnant females. Details regarding choice of cART regimen in pregnant HIV-infected women, including adolescents, are provided in the Perinatal Guidelines.[5] Although information is limited about the pregnancies of adolescents who were HIV-infected perinatally, perinatal HIV transmission outcomes in this population appear similar to those in adult cohorts;[15-18] however, there may be differences in pregnancy-related morbidities. Kenny et al[19] reported pregnancy outcomes from the United Kingdom and Ireland in a group of 30 adolescents who were perinatally HIV-infected or who acquired HIV infection at a young age. Few of these pregnancies were planned and in many cases, the partner was unaware of the mother's HIV status. Rates of elective termination, miscarriage, and prematurity were high. The rate of prematurity was twice that in the general adolescent population of Europe. Many of the women had an AIDS diagnosis before pregnancy, but only one infant was HIV-infected. Although the rate of perinatal transmission is reassuring, this study highlights some of the major challenges in caring for pregnant, perinatally HIV-infected youth.

Comparisons of pregnancy incidence and outcomes between perinatally infected and non-perinatally infected youth are few and may offer special insight into the effects of prolonged HIV infection on pregnancy-related sequelae. Agwu et al[20] retrospectively evaluated pregnancies at four clinics. Non-perinatally infected youth were more likely to have one or more pregnancies despite similar age at first pregnancy between groups. They also appeared to have more premature births and spontaneous abortions, but that is tempered by the fact that the perinatally infected youth were more likely to have an elective termination. The perinatal transmission rate for the entire cohort was 1.5%. Similar results were found in several other studies.[21,22] However, in a single-center review of perinatal versus non-perinatal birth outcomes, infants born to women with perinatal HIV infection were more likely to be small for gestational age.[23]

Transition of Adolescents into Adult HIV Care Settings

Facilitating a smooth transition of adolescents with chronic health conditions from their pediatric/adolescent medical home to adult care can be difficult and is especially challenging for HIV-infected adolescents. Transition is described as "a multifaceted, active process that attends to the medical, psychosocial, and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system."[24] Care models for children and adolescents with perinatally acquired 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 he or she often does not have a long-standing relationship. Providing an adolescent and an adult medical care provider with support and guidance regarding expectations for each partner in the patient-provider relationship may be helpful. In this situation, it may also be helpful for a pediatric and an adult provider to share joint care of a patient for a period of time. Providers should also have a candid discussion with a transitioning adolescent to understand what qualities the adolescent considers most important in an adult care setting (e.g., confidentiality, small clinic size, after-school appointments). Some general guidelines about transitional plans and who might benefit most from them are available.[25-30] Pediatric and adolescent providers should have a formal plan to transition adolescents to adult care.

Outcomes are variable in young adult patients transitioned to adult care. In a recent study, 10% of 18-year-olds were lost to follow-up with care at an adult HIV site associated with a greater likelihood of attrition.[31] Definitions of "successful transition" have ranged from the ability to maintain a certain level of follow-up in the new clinic, to laboratory measures of stability, to comparisons of younger and older adult patients.[32-34] Factors that should be taken into consideration 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. Currently there is no definitive model of transition to adult care, but in one study, adherence to medical visits just prior to the transition was predictive of successful transfer.[32] Psychiatric comorbidities and their effective management also predict adherence to medical care and therapy.[35-37]

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated February 12, 2014; last reviewed February 12, 2014)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of combination antiretroviral therapy (cART) and again before changing regimens **(AIII)**. • Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**. • At least one method of measuring adherence to cART should be used in addition to monitoring viral load **(AII)**. • When feasible, a once-daily antiretroviral regimen should be utilized **(AI*)**. • 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 combination antiretroviral therapy (cART) is a principal determinant of virologic suppression.[1-4] 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.[5] Based on early work in HIV-infected adults treated with unboosted protease inhibitor (PI)-based regimens,[2] ≥95% adherence has been the threshold associated with complete viral suppression. More recent studies from adult populations suggest that the relationship between ARV adherence and viral suppression may vary with individual drug, drug class, and pattern of adherence.[6] Viral suppression may be achieved with lower levels of adherence to boosted PI and non-nucleoside reverse transcriptase inhibitor regimens.[6,7] In patients who achieve virologic suppression, the longer the duration of suppression the lower the level of adherence necessary to prevent viral rebound.[8] Different patterns of inadequate adherence (intermittent missed doses, treatment interruptions) may have a differential impact on regimen efficacy, depending on the drug combination.[9,10]

Poor adherence can 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.[11] 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 ARVs is commonly encountered in the treatment of HIV-infected children and adolescents. Multiple studies have reported that less than 50% of children and/or caretakers reported full adherence to prescribed regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), ARV regimens, and study characteristics.[3,4,12-14] A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial and behavioral characteristics of children and parents have been associated with adherence; however, no consistent predictors of either good or poor adherence in children have been consistently identified.[12,15-19] Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.[20] These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to ensure adherence education, support, and assessment as integral components of care.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient and family factors, and characteristics of health care providers.[17] The limited availability of palatable formulations for young children is especially problematic.[5,21] Furthermore, infants and children are dependent on others for administration of medication; 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.[22,23] Some caregivers may place too much responsibility for managing medications on older children before they are developmentally able to undertake such tasks,[24] whereas others themselves face health and adherence challenges related to HIV infection or 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, avoidance 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, and involvement with the criminal justice system).

Specific Adherence Issues in Adolescents

HIV-infected adolescents also face specific adherence challenges.[25,26] Several studies have identified pill burden as well as lifestyle issues (i.e., not having medications on hand when away from home, change in schedule) as significant barriers to effective adherence.[15,27] Denial and fear of their HIV infection are common in adolescents, especially youth who have been recently diagnosed; this may lead to refusal to initiate or continue cART. Distrust of the medical establishment, misinformation about HIV, and lack of knowledge about the availability and effectiveness of ARV treatments can also be barriers to linking adolescents to care, retaining them in care, and maintaining them on successful cART.

Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they often have long histories of inadequate adherence. Regimen fatigue also has been identified as a barrier to adherence in adolescents.[28] HIV-infected adolescents often have low self-esteem, unstructured and chaotic lifestyles, concomitant mental illnesses, and cope poorly with their illness. Depression, alcohol or substance abuse, poor school attendance, psychiatric disorders and advanced HIV disease have been associated with nonadherence.[25,29-31] A review of published papers on adherence among HIV-infected youth suggests that depression and anxiety are consistently associated with poorer adherence.[29] Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties include adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and youth who are homeless and have no place to store medicine. When recommending treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ARV regimen with a realistic assessment of existing and potential support systems to facilitate adherence.

Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom cART 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 side effects of ARVs, such as nausea, headaches, and abdominal discomfort that may recede over time or respond to change in diet or timing of medication administration.

Adherence is difficult to assess accurately; different methods of assessment have yielded different results (and each approach has limitations).[14,32,33] Patients, caregivers, and health care providers often overestimate adherence. Use of multiple methods to assess adherence is recommended.[33,34] Viral load response to a new regimen is often the most accurate indication of adherence. 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. Caregivers may report number of doses taken more accurately than doses missed.[35] Targeted questions about stress, pill burden, and daily routine are recommended.[36,37] Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports.[38] Electronic monitoring devices (e.g., Medication Event Monitoring System [MEMS] caps) which are equipped with a computer chip that records each opening of a medication bottle are primarily used in research studies, but have been shown to be useful tools to measure adherence in some settings.[39-41] Mobile phone technologies (e.g., interactive voice response, SMS text messaging), are being evaluated to quantify missed doses and provide real-time feedback on adherence to caregivers, but studies in the pediatric population are in the pilot phase.[42] Home visits can play an important role in assessing adherence. In some cases, suspected non-adherence is confirmed only when dramatic clinical responses to cART occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma ARV concentrations or therapeutic drug monitoring may be useful measures in situations where non-adherence is suspected.[43] Drug concentrations in hair are currently being studied as an alternative method to measure adherence.[44,45]

Adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both HIV-infected children and their caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources.[46]

Strategies to Improve and Support Adherence

Intensive follow-up is required, particularly during the first few months after therapy is initiated. Patients should be seen frequently—as often as weekly during the first month of treatment—to assess adherence and determine the need for strategies to improve and support adherence. Strategies include 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.[24,47,48] Programs designed for administration of directly observed combination therapy to adults, in either the clinic or at home, have demonstrated successful results in both the United States and in international, resource-poor settings.[49-51] Modified directly observed therapy (m-DOT), where one dose is administered in a supervised setting and the remaining doses are self-administered, appears to be both feasible and acceptable.[47,52] However, a recent meta-analysis of 10 randomized clinical trials evaluating DOT to promote adherence in adults found that it was no more effective than self-administered treatment.[53] In another meta-analysis of DOT studies, DOT was found to have a demonstrated effect on virologic, immunologic, and adherence outcomes, but efficacy of the strategy was not supported when the analysis was restricted to randomized controlled trials.[54] Table 10 summarizes some of the strategies that can be used to support and improve adherence to ARV medications.

Regimen-Related Strategies

ARV regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side 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 side effects.[55] When non-adherence occurs, addressing medication-related issues (.e.g., side effects), may result in improvement. If a regimen is overly complex, it can be simplified. For example, when the burden of pills is great, one or more drugs can be changed to a fixed-drug combination resulting in a regimen with fewer pills. When feasible, a once-daily regimen should be recommended. Several studies in adults have demonstrated better adherence with once-daily versus twice-daily ARV regimens.[56-60] When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can sometimes be masked with a small amount of flavoring syrup or food (see Appendix A: Pediatric Antiretroviral Drug Information) or a child can be taught to swallow pills in order to overcome medication aversion.[61] Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup.

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 for taking medications, can be effective tools to promote adherence.[62,63] Training children to swallow pills has been associated with improved adherence at 6 months post-training in a small study of children aged 4 to 21 years.[64] Availability of mental health services and the treatment of mental health disorders may facilitate adherence to complex ARV regimens. 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.[65] If adequate resources are available, home-nursing interventions also may be beneficial.[66] Directly observed dosing of ARV medications has been implemented in adults, adolescents, and children, using home nursing services as well as daily medication administration in the clinic setting.

Other strategies to support adherence that have been employed in the clinical setting 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 and other adherence support tools, particularly for patients with complex regimens; and delivering medications to the home. Two randomized clinical trials in adults have demonstrated that SMS text-messaging, at weekly intervals, is associated with improved adherence outcomes.[67-69] In a pilot study evaluating peer support and pager messaging in an adult population, peer support was associated with greater self-reported adherence post-intervention; however, the effect was not sustained at follow-up. Although pager messaging was not associated with reported adherence, improved biologic outcomes were measured.[70] A study evaluating the efficacy of a 4-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 cART. However, reduction in viral load was not maintained at 9 months.[71]

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.[72,73] 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.[74]

Table 10. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on 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. Treat mental health issues before starting antiretroviral (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. • Specify the adherence target: ≥95% of prescribed doses. • Educate patient and family about the relationship between partial adherence and resistance. • Educate patient and family about resistance and constraint in later choices of ARV drug (i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent). • 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. • 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. • Choose a regimen with dosing requirements that best conform to 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 side effects; provide anticipatory guidance for management of side effects. • Simplify food requirements for medication administration. • Prescribe drugs carefully to avoid adverse drug-drug interactions. • Assess pill-swallowing capacity and offer pill-swallowing training.
Follow-up Intervention Strategies
• Monitor adherence at each visit and in between visits by telephone or letter, as needed. • Provide ongoing support, encouragement, and understanding of the difficulties associated with demands to attain 95% adherence with medication doses. • 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 SMS 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 directly observed therapy at home, in the clinic, or in selected circumstances, during a brief inpatient hospitalization. • Consider gastrostomy tube use in selected circumstances.

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Management of Medication Toxicity or Intolerance (Last updated February 12, 2014; last reviewed February 12, 2014)

Overview

Panel's Recommendations
• In children who have severe or life-threatening toxicity, all antiretroviral (ARV) drugs should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, ARV therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) **(AII*)**. • When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; 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 when therapeutic drug monitoring indicates a drug concentration above the normal therapeutic range **(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 combination antiretroviral therapy (cART) 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 cART regimen, as well as the individual child's underlying conditions, concomitant medications, and prior history of drug intolerances or viral resistance.

Adverse effects 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 adverse events 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 cART regimens and are generally less than 10%.[1-4] In general, the overall benefits of cART outweigh its risks, and the risk of some abnormal laboratory findings (e.g., anemia, renal impairment) may be lower with cART than in its absence.

ARV drug-related adverse events 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.[5] For selected children aged <3 years who require treatment with efavirenz, an additional pharmacogentic marker, CYP2B6 genotype, should be assessed (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).[6]

The most common acute and chronic adverse effects 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 adverse effects 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 adverse effects. Common, self-limited adverse effects should be anticipated, and reassurance provided that many adverse effects will resolve after the first few weeks of cART. For example, when initiating therapy with boosted protease inhibitors (PIs) many patients experience gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these side effects. Some patients may require antiemetics and antidiarrheal agents for symptom management. Central nervous system (CNS) adverse effects 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 to help minimize these adverse effects and be advised that these side effects should diminish or disappear within 2 to 4 weeks of initiating therapy in most people. 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 an unacceptable adverse effect from cART, every attempt should be made to identify the offending agent and replace the drug with another effective agent as soon as possible.[1,7]. Although many experts will stagger a planned interruption of a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART regimen, stopping the NNRTI first and the dual nucleoside analogue reverse transcriptase backbone 7-14 days later because of the long half-life of NNRTI drugs , in patients who have a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the adverse event 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 adverse effects.

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.[8-12] 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 virololgic 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).

Therapeutic drug monitoring (TDM) may be used in the management of the child with mild or moderate toxicity if the toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range[13,14] (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.

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 sensitive (such as changing to abacavir for zidovudine-related anemia or to nevirapine for efavirenz-related CNS symptoms).
- Change drug class, if necessary (such as from a PI to a non-nucleoside reverse transcriptase inhibitor or vice versa) and if a patient's virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.

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Table 11a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated February 12, 2014; last reviewed February 12, 2014) (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 • Cardiac toxicity • Respiratory complications	Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates.	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.
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	Onset: • 1–2 days after initiating treatment • Most symptoms subside or diminish by 2–4 weeks, but may persist in a minority of patients. Presentation *May Include One or More of the Following:* • Dizziness • Somnolence • Insomnia • Abnormal dreams • Impaired concentration • Psychosis • Suicidal ideation • Seizures (including absence seizures) or decreased seizure threshold. Note: Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.	Variable, depending on age, symptom, assessment method Children: • 24% for any EFV-related CNS manifestations in one case series with 18% requiring drug discontinuation • In one report, 4/44 (9%) of young HIV-infected children aged <36 months experienced new onset seizures within 2–9 weeks of initiating EFV, although 2 of them had an alternative cause for the seizures. Adults: • >50% for any CNS manifestations of any severity • 2% for EFV-related severe CNS manifestations	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 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).	Provide reassurance about the likely time-limited nature of symptoms. Consider EFV trough level if symptoms excessive or persistent. If EFV trough level >4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug substitution. In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time.

Table 11a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated February 12, 2014; last reviewed February 12, 2014) (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	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	Pre-screen 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.
	RPV	Presentation: • Dizziness • Abnormal dreams/nightmare • Insomnia	In Adults: • 43% all grade neuropsychiatric AE at 96 weeks (mostly Grade 1, causing RPV discontinuation in only one case, significantly lower than EFV)	Prior history of neuropsychiaric illness	Monitor carefully for CNS symptoms.	Consider drug substitution in case of severe symptoms.
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 patient-years or 0.04–0.22/100 patient years 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.

Table 11a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated February 12, 2014; last reviewed February 12, 2014) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
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: AE = adverse effect; ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxyl fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucurononyl transferase

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Table 11b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia
(Last updated February 12, 2014; last reviewed February 12, 2014) (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 ritonavir 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	10% to 20% in young children receiving LPV/RTV 20% to 50% of children receiving ART will have lipoprotein abnormalities.	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 • No smoking Monitoring *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).	Assessment of additional CVD risk factors should be done in all patients. HIV-infected patients are considered to be at moderate risk of CVD.[a] Counsel lifestyle modification, dietary interventions (e.g., low-fat diet; low simple carbohydrate diet in case of ↑TG; exercise, smoking cessation) for adequate trial period (3–6 months). Pharmacologic Management: • Dyslipidemic children aged ≥10 years with LDL-C ≥250 mg/dL or TG levels ≥500 mg/dL and all children aged <10 years who require lipid-lowering treatment should be managed by a lipid specialist. Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with antiretroviral treatment.[b] Risks must be weighed against potential benefits Consider switching to a new ART regimen less likely to cause lipid abnormalities. Consider lipid-lowering therapy in consultation with a lipid specialist if 6-month trial of lifestyle modification fails. No consensus exists as to what

Table 11b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated February 12, 2014; last reviewed February 12, 2014) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
					Children Receiving Lipid-Lowering Therapy with Statins or Fibrates: • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 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 month thereafter (or as clinically indicated). • Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.	LDL-C should prompt treatment in children receiving ARV drugs. Drug therapy cut points recommended by NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL–C ≥190 mg/dL, regardless of additional risks factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.[a] The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL. <u>Initiate Drug Therapy Promptly in Patients with TG ≥500 mg/dL</u>: • Statins such as pravastatin, atorvastatin, or rosuvastatin.[b] Ezetimibe can be considered in addition to statins.[c] 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 cART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.

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

[b] 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.

[c] 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

Key to Acronyms: ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; cART = combination antiretroviral therapy; CK = creatine kinase; CVD = cardiovascular disease; DRV/r = darunavir/ritonavir; d4T = stavudine; EFV = efavirenz; FLP = Fasting Lipid Profile; HDL-C = high-density lipoprotein cholesterol; non-HDL-C= non-high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; LFT = liver function test; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; TC = total cholesterol; TG = triglyceride; RTV=ritonavir; ETR=etravirine

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Table 11c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated February 12, 2014; last reviewed February 12, 2014)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (such as LPV/r, RTV) but can occur with all ARVs	Onset: • Early Presentation: • Nausea, emesis—may be associated with anorexia and/or abdominal pain.	Varies with ARV agent; 10%–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 (NFV, LPV/r, FPV/r), buffered ddI	Onset: • Early Presentation: • Generally soft, more frequent stools	Varies with ARV agent; 10%–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 for ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate, 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).	<1%–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; d4T = stavudine; ddI = didanosine; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; LPV = lopinavir; 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 11d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated February 12, 2014; last reviewed February 12, 2014) (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 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 • Concurrent ZDV plus 3TC neonatal prophylaxis HIV-Infected Children on ARVs: • Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease	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)	>90-95%, all ages	None	Obtain CBC as part of routine care	None required unless associated with anemia

Table 11d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated February 12, 2014; last reviewed February 12, 2014) (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: • 9.9%–26.8% of children on ARVs, depending upon the ARV regimen • Highest rates with ZDV-containing regimens	HIV-Exposed Newborns: • In utero exposure to ARVs • Concurrent ZDV plus 3TC neonatal prophylaxis 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 Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV marrow-toxic drugs, if feasible. • Treat co-existing 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; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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Table 11e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated February 12, 2014; last reviewed February 12, 2014) (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 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 [*Teudrium 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., as 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. If ALT or AST >5 to 10 times ULN, some would consider discontinuing ARVs. 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, and ZDV, d4T, and ddI in particular (see also Lactic Acidosis). Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 11e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated February 12, 2014; last reviewed February 12, 2014) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Indirect Hyperbilirubinemia	IDV, ATV	Onset: • First months of therapy Presentation: • Jaundice; otherwise asymptomatic elevation of indirect bilirubin levels with normal direct bilirubin, AST, and ALT.	HIV-Infected Children Receiving ATV: • 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.	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	ARVs, especially ddI, d4T, and combination of ddI and 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] E.g. HLA-DRB1*0101 in Caucasians, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and Caucasians

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; 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; IDV = Indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

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Table 11f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated February 12, 2014; last reviewed February 12, 2014)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	Thymidine analogue NRTIs (i.e., d4T, ddI, ZDV) Several PIs (i.e., IDV, LPV/r; less often ATV, ATV/r, DRV/r, 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 Children:* • 6%–33% Impaired Fasting Glucose: *ARV-Treated Adults:* • 3%–25% *ARV-Treated Children:* • 0%–7% Impaired Glucose Tolerance: *ARV-Treated Adults:* • 16%–35% *ARV-Treated Children:* • 3%–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:* • Very 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, IDV may reduce risk. Monitoring: • Monitor for polydipsia, polyuria, polyphagia, change in body habitus, and acanthosis nigricans. *Obtain RPG levels at:* • Initiation of ARV therapy, and • 3–6 months after therapy initiation, and • 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 (i.e., low-fat diet, exercise, no smoking). Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen. 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 standard OGTT; 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: ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; d4T = stavudine; ddI = didanosine; DM = diabetes mellitus; DRV/r = ritonavir-boosted darunavir; FPG = fasting plasma glucose; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

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Table 11g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis
(Last updated February 12, 2014; last reviewed February 12, 2014)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic Acidosis	NRTIs, in particular, d4T and ddI (highest risk in combination)	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 (such as fulminant hepatic, pancreatic, and respiratory failure).	Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L) *Adults:* • 15%–35% of adults receiving NRTI therapy for longer than 6 months *Children:* • 29%–32% Symptomatic Severe Hyperlactatemia (>5.0 mmol/L) *Adults:* • 0.2%–5.7% Symptomatic Lactic Acidosis/Hepatic Steatosis: • Rare in all age groups (1.3–11 episodes per 1,000 person-years; increased incidence with the use of d4T/ddI in combination), but associated with a high fatality rate (33%–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: • Use of propylene glycol (e.g., as an diluent for LPV/r)	Prevention: • Avoid d4T and ddI individually and especially in combination in an ARV regimen. • 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 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 = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; TDF = tenofovir disoproxil fumarate; THAM = tris(hydroxymethyl)aminomethane

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Table 11h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated February 12, 2014; last reviewed February 12, 2014)

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 cART; peripheral fat wasting may not begin to appear for 12 to 24 months after cART initiation.	Highly Variable Adults: • 2%–93% Children: • 1%–34%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of cART Body habitus	See below.	See below.
Central Lipohypertrophy or Lipoaccumulation	Can occur in the absence of cART, but most associated with PIs and EFV; EFV also associated with gynecomastia and breast hypertrophy	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. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Children: • Up to 27% Adults: • 6 to 93%	Obesity before initiation of therapy Sedentary lifestyle	Prevention: • Calorically appropriate low-fat diet and exercise. Monitoring: • Measure BMI.	Calorically appropriate low-fat diet and exercise, especially strength training. Smoking cessation (if applicable) to decrease future CVD risk. 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, or liposuction.
Facial/Peripheral Lipoatrophy	Most associated with thymidine analogues NRTI (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.	Children: • Up to 47% (particularly in patients on d4T-containing regimens) • Risk lower (up to 15%) in patients not treated with d4T or ZDV Adults: • 13% to 59% (particularly in patients on d4T-containing regimens)	d4T and ZDV Underweight before cART	Prevention: • Avoid use of d4T and ZDV. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Switch from d4T or ZDV to 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: ARV = antiretroviral; BMI = body mass index; cART = combination antiretroviral therapy; 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 11i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated February 12, 2014; last reviewed February 12, 2014) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ Nephrolithiasis	IDV, ATV	Onset: • Weeks to months after starting therapy Clinical findings: • Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%). ATV nephrolithiasis is rare.	In adults, high serum IDV concentrations and elevated urine pH (>5.7) associated with persistent pyuria. 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. Presentation *More Common:* • Increased serum creatinine, proteinuria. 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: • ~2% with increased serum creatinine • ~0.5% with severe renal complications Children: • ~4% with hypophosphatemia or proximal tubulopathy; higher in advanced HIV infection or concomitant use of ddI	Risk May Be Increased in Children: • aged >6 years • of Black race, Hispanic/Latino ethnicity • with advanced HIV infection • with concurrent use of ddI or PIs (especially LPV/r), and pre-existing renal dysfunction • Risk increases with longer duration of TDF treatment.	Monitor urine protein and glucose or urinalysis, and serum creatinine at intervals of every 3–6 months. 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 monitor 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.

Table 11i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated February 12, 2014; last reviewed February 12, 2014) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Renal Dysfunction, continued	IDV	Renal cortical atrophy, acute renal failure	Rare	Unknown	Unknown	If IDV is likely cause, consider using alternative ARV. **Note:** IDV not FDA-approved for use in children.

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ddI = didanosine; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

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Table 11j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated February 12, 2014; last reviewed February 12, 2014)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and Osteoporosis	cART, especially following initiation and regardless of regimen Specific Agents of Possible Concern: • TDF • d4T • PIs, especially LPV/r	Onset: • Any age; greatest risk in months after initiation of associated ARV 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 of ≤ –2.0 (87% treated with cART). • 24% to 32% of Thai and Brazilian adolescents had a BMD z score of ≤ –2.0 (92% to 100% treated with cART).	Longer duration of HIV infection Greater severity of HIV disease Growth delay, pubertal delay Low BMI Lipodystrophy Non-black race Smoking Corticosteroid use Medroxyprog-esterone use	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). • Obtain serum 25-OH-vitamin D.[a] • Obtain DXA.[b]	Ensure sufficient calcium and vitamin D intake. Encourage weight-bearing exercise. Reduce modifiable risk factors (e.g., smoking, low BMI, use of steroids, 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 this 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 should also be obtained in children with indications not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; cART = combination antiretroviral therapy; d4T = stavudine; DXA = dual energy x-ray absorptiometry; LPV/r = lopinavir / ritonavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

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Table 11k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated February 12, 2014; last reviewed February 12, 2014)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency[a]	Risk Factors	Prevention/ Monitoring	Management
ARV Toxic Neuropathy[b]	d4T, ddI	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). HIV-Infected Adults on d4T: • Prevalence up to 57% • Incidence rates 6.4–12.1 per 100 person-years	HIV-Infected Adults: • Pre-existing 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, if possible. 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. Data are Insufficient to Allow the Panel to Recommend Use of any of the Following Modalities in Children: • tricyclic antidepressants • gabapentin • pregabalin • mexilitine • lamotrigine Consider referral to neurologist.

[a] Peripheral neuropathy may be under-reported 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

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Table 11I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated February 12, 2014; last reviewed February 12, 2014) (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 HSR, SJS/TEN/EM major).	Common (>10% Adults and/or Children): • NVP, EFV, ETR, FPV, ATV, FTC Less Common (5%–10%): • ABC, DRV, TPV, TDF Unusual (2%–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 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 Mucus 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, pruritis, ecchymosis. Often multiple reactions at the same time.	Adults and Children: • >90%	Unknown	• During routine visits, assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient. • Adjust injection technique. • Rotate injection sites.

Table 11I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated February 12, 2014; last reviewed February 12, 2014) (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)	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] • 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.
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 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.	2.3%–9% (varies by racial/ethnic group).	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701 negative); also HLA-DR7, HLA-DQ3. • HSR risk is higher in those of White race compared to those of Black or East Asian race.	• 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 and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms (e.g, a concurrent viral illness). • 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.

Table 11l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated February 12, 2014; last reviewed February 12, 2014) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involvement and excluding SJS/TEN	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. • DRESS syndrome has also been described.	4% (2.5%–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 prepubertal 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 reintroduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.
	ENF, ETR	Onset: • 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.

Table 11I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated February 12, 2014; last reviewed February 12, 2014) (page 4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involvement and excluding SJS/TEN	RAL	DRESS syndrome	Case report	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARVs. Rechallenge with RAL 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.

[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 February 12, 2014; last reviewed February 12, 2014)

Overview

In the United States, the vast majority of HIV-infected children are receiving combination antiretroviral therapy (cART), 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 cART for simplification or improved adverse effect 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 Recommendation
• For children who have sustained virologic suppression on their current regimen, changing to a new antiretroviral regimen with improved pill burden or tolerance should be considered in order to facilitate continued adherence and increase safety **(BII)**.
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 cART. 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 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 effects, 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 (aged <3 years) with virologic suppression who switch from ritonavir-boosted lopinavir to nevirapine can maintain virologic suppression as well as those who continue ritonavir-boosted lopinavir, provided there is good adherence and no baseline resistance to nevirapine.[1,2] By extrapolation, replacement of ritonavir-boosted lopinavir with efavirenz, another non-nucleoside reverse transcriptase inhibitor (NNRTI), another protease inhibitor, raltegravir, or another integrase inhibitor would likely be effective, but this 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 or zidovudine; replacing protease inhibitor with NNRTI), including improved lipid profiles, in small cohorts of children.[3-7] Small studies have shown that children with virologic suppression on twice-daily regimens maintain virologic suppression if abacavir dosing is changed from twice daily to once daily (see Abacavir drug section) but show mixed results when switching ritonavir-boosted lopinavir dosing from twice daily to once daily.[8,9]

Table 12 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 ARV treatment failure and all prior drug resistance testing results in order to avoid choosing new ARV drugs for which archived drug resistance would limit activity. 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 is important to ensure that virologic suppression is maintained.

Table 12: 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

ARV Drug(s)	Current Age	Body Size Attained	Potential ARV Regimen Change	Comment
ZDV or ddI (or d4T*)	≥1 year	N/A	ABC	Once-daily dosing (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Less long-term mitochondrial toxicity.
ABC Twice Daily	≥1 year	Any	ABC once daily	See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for full discussion.
LPV/r	≥1 year	≥3 kg	RAL	Better palatability. Less adverse lipid effect.
LPV/r Twice Daily	≥3 years	N/A	EFV	Once-daily dosing. Better palatability. Less adverse lipid effect. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children < 3 years old.
LPV/r Twice Daily	≥6 years	15 kg	ATV/r	Once-daily dosing. Lower pill burden. Less adverse lipid effect
ZDV or ddI	Adolescence	Pubertal maturity (Tanner IV or V)	TDF or ABC	Once-daily dosing. Less long-term mitochondrial toxicity. Coformulation with other ARVs can further reduce pill burden.
LPV/r Twice Daily	≥12 years	40 kg	DRV/r	Once-daily dosing possible. Lower pill burden.
Any	Adolescence	• Pubertal maturity (Tanner IV or V)	Co-formulated: • TDF-FTC-EFV • EVG-COBI-FTC-TDF • FTC-RPV-TDF	Once-daily dosing. Single pill. Alignment with adult regimens.

* Because of concerns about long-term adverse effects, d4T may be replaced by a safer drug even before sustained virologic suppression is achieved (see Stavudine in Appendix A: Pediatric Antiretroviral Drug Information).

Key to Acronyms: ABC = abacavir; ATV/r = ritonavir-boosted atazanavir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = ritonavir-boosted darunavi; EFV = efavirenz, EVG = elvitegravir; FTC = emtricitabine; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; TDF = tenofovir disoproxil fumarate, ZDV = zidovudine

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Recognizing and Managing Antiretroviral Treatment Failure (Last updated February 12, 2014, last reviewed February 12, 2014)

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

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 HIV RNA below the level of quantification using the most sensitive assay (<20 to 75 copies/mL). Older assays with lower limits of 200 or 400 copies/mL are not recommended. **Virologic failure** is defined for all children as a plasma HIV RNA >200 copies/mL after 6 months of therapy or repeated plasma HIV RNA greater than the level of quantification using the most sensitive assay after 12 months of therapy. Occasionally, infants with high plasma HIV RNA levels at initiation of therapy have HIV RNA levels that are declining but remain >200 copies/mL after 6 months of therapy. Among many of those receiving ritonavir-boosted lopinavir, suppression can be achieved without regimen change if efforts are made to improve adherence.[1] However, ongoing non-suppression—especially with non-nucleoside reverse transcription inhibitor (NNRTI)-based regimens—increases risk of drug resistance.[2] HIV-infected adults with detectable HIV RNA and a quantified result <200 copies/mL after 6 months of combination antiretroviral therapy (cART) often ultimately achieve virologic suppression without regimen change.[3] "Blips," defined as isolated episodes of plasma HIV RNA <500 copies/mL followed by return to viral suppression, are common and not generally reflective of virologic failure.[4-6] Repeated or persistent plasma HIV

RNA detection above the level of quantification (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.[6-8]

Immunologic Failure

Immunologic failure is defined as an incomplete immunologic response to therapy or an immunologic decline while on therapy. While there is no standardized definition, many experts would consider as incomplete 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 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 cART initiation often do not represent cART failure. For example, the development or worsening of an OI in a patient who recently initiated cART 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, 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, cART 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 cART that fails to suppress viremia is commonly accompanied by immunologic and clinical failure.[9] However, patients may also present with failure in one domain (e.g., immunologic failure) but with a good response in the other domains (e.g., virologic and clinical response). In fact, the discordance in responses to cART can occur in any of these three domains in relation to the other two. It is essential to consider potential alternative causes of discordant responses before concluding that cART failure has truly occurred.

Incomplete Virologic Response Despite Adequate Clinical and Immunologic Responses

Some patients who are maintained on cART may sustain immunologic and clinical benefit for up to 3 years despite persistent low-level viremia.[10-19] This observation is the rationale for continuing non-suppressive cART for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practical. The proposed mechanisms for immunologic and clinical benefit without complete virologic suppression are maintenance of a lower viral load or selection for strains harboring drug-resistance mutations that impair viral replicative capacity or fitness. Another potential explanation for this discordance is that some of these children may have host genetic and/or virologic characteristics that would have allowed them to be either “slow-progressors” or “long-term non-progressors” without therapy.

Poor Immunologic Response Despite Virologic Suppression Regardless of Clinical Response

Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. 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 count over the first 5 to 6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (such as HIV-1 non-M groups or non-B subtypes, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection and Clinical and Laboratory Monitoring). Once lab results are confirmed, evaluation for adverse drug effects, medical conditions, and other factors that can result in lower CD4 values is necessary (see Table 13).

In addition, it is common for patients with baseline severe immunosuppression to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in a transient early treatment period of persistent immunosuppression during which additional clinical disease progression can occur. Patients who have very low baseline CD4 values before initiating cART are at higher risk of an impaired CD4 response to cART and, based on adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.[20-24]

Certain antiretroviral (ARV) agents or combinations may be associated with a blunted CD4 response. For example, treatment with a regimen containing tenofovir disoproxil fumarate (tenofovir) and didanosine can blunt the CD4 response, especially if the didanosine dose is not reduced,[25] and this combination is not recommended as part of initial therapy. Dosing of didanosine should be reduced when co-administered with tenofovir. 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.[26] 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, 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 immunological and virological responses to cART. Not all cases represent cART 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 cART is IRIS, which does not represent cART failure and does not generally require discontinuation of cART.[27,28] 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.[29] Such cases do not represent cART failure and, in these instances, children would not benefit from a change in ARV regimen. Before reaching a definitive conclusion of cART clinical failure, a child should also be evaluated to rule out (and, if indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary tuberculosis, malnutrition, and malignancy. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason. Although such cases are rare, they may represent cART clinical failure and suggest that improvement in CD4 values may not necessarily represent the return of complete immunologic function.

Table 13: 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) • Normal age-related CD4 decline (i.e., immunologic response not actually poor) • Low pretreatment CD4 cell count or percentage • Adverse effects of use of zidovudine or the combination of tenofovir and didanosine • Use of systemic corticosteroids or chemotherapeutic agents • Conditions that can cause low CD4 values, such as hepatitis C coinfection, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis *Poor Immunologic and Clinical Responses Despite Virologic Suppression:* • Lab error, including 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 cART but before cART-related reconstitution • Primary protein-calorie malnutrition • Untreated tuberculosis • Malignancy • Loss of immunologic (CD4) reserve
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
• IRIS • Previously unrecognized pre-existing infection or condition (tuberculosis, malignancy) • Malnutrition • Clinical manifestations of previous organ damage: brain (strokes, vasculopathy), lungs (bronchiectasis) • New clinical event due to non-HIV illness or condition • New, otherwise unexplained HIV-related clinical event (treatment failure)

Key to Acronyms: cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; IRIS = immune reconstitution inflammatory syndrome

Management of Virologic Treatment Failure

Each patient with incomplete virologic suppression on cART should be assessed to determine the cause of virologic treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. Treatment failure is generally the result of non-adherence but is often multifactorial. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, issues related to pharmacokinetics (PK) that could result in low drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance (See Antiretroviral Drug-Resistance Testing). 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 14 outlines a comprehensive approach to evaluating causes of virologic treatment failure in children, with particular attention to adherence.

Table 14. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 1 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention

Non-Adherence	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
	• Have open-ended discussion of experiences taking/giving medications and barriers/challenges
	2. Review pharmacy records
	• Assess timeliness of refills
		• Identify or re-engage 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 co-formulated under a third or fourth name
		• Explore opportunities for facility or home-based DOT

	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 gastric tube placement to facilitate adherence
		• Consider DOT
		• Use tools to simplify administration (e.g., pill boxes, reminders [including alarms], integrated medication packaging for a.m. or p.m. dosing)

	4. Conduct psychosocial assessment
	• Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes:
	  • 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 cART
	  • 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 body surface area 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

Table 14. 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).	• If no resistance to current drugs is detected, focus on improving adherence • If resistance to current regimen detected, optimize adherence and evaluate potential for new regimen (see *Management of Virologic Treatment Failure*)

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, 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 suggests that the virus is not being exposed to the ARV agents. This lack of ARV drug exposure is usually a result of non-adherence, 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). 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 plasma virus is undetectable with the most sensitive assays, the virus is likely to be susceptible to the current therapy.

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, some clinicians may choose to continue the current non-suppressive regimen or use a simplified, nucleoside reverse transcriptase inhibitor (NRTI)-only, non-suppressive regimen that may provide some clinical and immunologic benefit while preserving future ARV drug choices (see *Therapeutic Options When Two Fully Active Agents Cannot Be Identified or Administered*).[30-32] 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. 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 non-adherent patient should prevent accumulation of additional drug resistance but has been associated with immunologic declines and poor clinical outcomes.[33]

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.[34-38] 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 should not be done because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency because of the presence of drug-resistance mutations that confer cross-resistance within a drug class. In children who are changing therapy owing to the occurrence or progression of abnormal neurodevelopment, many experts strive to include in the new treatment regimen agents (e.g., zidovudine) that are known to achieve higher concentrations in the central nervous system.[39-43]

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.[44]

Choice of Therapy 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 in collaboration with a pediatric HIV specialist. ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug potency in the new regimen. A general strategy for regimen change is shown in Table 15, 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 a NNRTI-based regimen, a change to a protease inhibitor (PI)-based regimen is recommended. Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. However, the NNRTI etravirine can retain activity against nevirapine- or efavirenz-resistant virus in the absence of certain key NNRTI mutations (see below). If a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is generally recommended. Ritonavir-boosted-lopinavir-based regimens have also been shown to have durable ARV activity in some PI-experienced children.[45-47]

The availability of new drugs in existing classes (e.g., the NNRTI etravirine) and newer classes of drugs (e.g., integrase inhibitors) increases the likelihood of finding three active drugs, even for children with extensive drug resistance (Table 15). Etravirine in combination with ritonavir-boosted darunavir, as part of a new cART regimen, has been shown to be a safe and effective option for children in whom first-line cART fails.[48,49] Etravirine is approved for use in children aged ≥6 years and darunavir in children aged ≥3 years. Raltegravir, an integrase inhibitor, is approved for children aged 4 weeks or older by the Food and Drug Administration (FDA).[50] Use of newer agents in novel combinations is becoming more common in aging perinatally infected youth in the United States.[51] It is important to review individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance. Appendix A: Pediatric Antiretroviral Drug Information provides more detailed information on drug formulation, pediatric and adult dosing, and toxicity, as well as discussion of available pediatric data for the approved ARV drugs.

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if ARV resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching from a liquid to a pill formulation or to a new formulation [e.g., ritonavir tablet]). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir.[52-54] 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.

Safety, dosing, and efficacy of enfuvirtide have been established in treatment-experienced children aged ≥6 years, and enfuvirtide has been FDA-approved for this population.[55,56] Enfuvirtide must be administered by subcutaneous injection twice daily, a disadvantage that presents a greater challenge to adherence in adolescents than in younger children. Enfuvirtide can be considered an option when designing a new regimen for children in whom multiple classes of ARV medications have failed, but newer and better tolerated agents have largely supplanted use of enfuvirtide.

PK studies of certain dual-boosted PI regimens (ritonavir-boosted lopinavir with saquinavir and ritonavir-boosted lopinavir with atazanavir/ritonavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in children.[57-59] PK studies of other dual-boosted PI combinations, on the other hand, are limited but suggest inadequate drug levels of one or both PIs.[60,61] The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series;[62] however, multidrug regimens should be used cautiously because of their complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity because of the presence of drug-resistance mutations (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). Availability of newer potent PIs and new classes of ARV drugs (integrase and CCR5 inhibitors) may lessen the need for dual-PI regimens and for regimens of four or more drugs.

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.[63] 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.[64]

Use of ARV agents without a pediatric indication is an absolute necessity for treatment of some HIV-infected children, but such off-label use must be done with care. It is essential that a provider consult with a pediatric HIV specialist to identify any particular concerns with each agent, to access any available data from clinical trials or other limited off-label pediatric use, and to investigate the availability of suitable clinical trials.

Therapeutic 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 cART.

In such cases, non-suppressive regimens (or holding regimens) are sometimes used pending availability of additional active, tolerable drugs or improvement in ability to adhere. This interim strategy allows for the overall objective of preventing clinical and immunological deterioration until new agents are available to design a regimen that can be expected to achieve sustained virologic suppression. This approach should be regarded as acceptable but not ideal. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive cART regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, patients can derive immunologic and clinical benefit despite persistent viremia from treatment with lamivudine monotherapy or with lamivudine or emtricitabine in combination with one or more other NRTIs.[31,32]

The newer NNRTI etravirine retains activity against many nevirapine- or efavirenz-resistant viruses with a limited number of NNRTI resistance-associated mutations. Ongoing use of efavirenz or nevirapine as part of a failing regimen should be avoided because it may lead to accumulation of additional NNRTI resistance mutations that will reduce etravirine activity and preclude its use in a future, suppressive regimen,[65] and it may allow for accumulation of additional NRTI resistance.[66]

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low.[2,67-69] However, continued PI use in the presence of resistance may limit viral replication and be beneficial to some patients.

When clinical or immunologic deterioration occurs while patients are receiving such holding regimens, it is important to reassess patient readiness and regimen availability. It may be appropriate to use investigational agents or agents approved for older age groups as second fully active drugs in the new regimen. In general, a single, new, fully active agent should not be added to non-suppressive holding regimens because resistance is likely to develop quickly.

Table 15. 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	Recommended Change (In Order of Relative Preference)[a]
2 NRTIs + NNRTI	• 2 NRTIs + PI • 2 NRTIs + integrase inhibitor
2 NRTIs + PI	• 2 NRTIs + NNRTI • 2 NRTIs + different RTV-boosted PI • 2 NRTIs + integrase inhibitor • NRTI(s) + integrase inhibitor + (NNRTI or different RTV-boosted PI)
3 NRTIs	• 2 NRTIs + (NNRTI or PI) • 2 NRTIs + integrase inhibitor • Integrase inhibitor + 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	• 1 NRTI + RTV-boosted PI • NRTI(s) + RTV-boosted PI + integrase inhibitor (consider adding T-20 and/or MVC,[b] if additional active drug[s] needed) • NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC,[b] T-20, or integrase inhibitor, if additional active drug[s] needed) • > 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor 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 listed in relative order of preference and 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, LPV = lopinavir, LPV/r = ritonavir- boosted lopinavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide

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Considerations About Interruptions in Antiretroviral Therapy (Last updated February 12, 2014, last reviewed February 12, 2014)

Panel's Recommendations
• Outside the context of clinical trials, structured interruptions of combination antiretroviral therapy are not recommended for children **(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*

Unplanned Interruptions:

Temporary discontinuation of combination antiretroviral therapy (cART) 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 parent 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]

Structured Treatment Interruptions

Planned discontinuation of therapy, or structured treatment interruptions, was considered as a potential strategy to reduce toxicity, costs, and drug-related failure associated with cART.

Adult trials have demonstrated significantly higher morbidity and mortality in adults randomized to structured treatment interruptions compared with continuous cART.[4] Current Department of Health and Human Services guidelines for adults recommend against planned long-term structured treatment interruptions in adults (see the Adult and Adolescent Antiretroviral Guidelines).

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.[5] However, new drug-resistance mutations were detected in 3 of 14 children in the structured treatment interruption study. In the European (PENTA) trial, 109 children with virologic suppression on cART were randomized to continuous therapy (CT) versus treatment interruption with CD4 T lymphocyte (CD4)-guided re-initiation of cART. On average, CD4 values decreased sharply in the first 10 weeks after structured treatment interruption. However, most children in the structured treatment interruption arm (almost 60%) did not reach CD4 criteria to restart therapy over 48 weeks. Children in the structured treatment interruption arm spent significantly less time on cART than children in the CT arm.[6] 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.[6]

In some populations of children, structured treatment interruption has been more specifically considered. One trial was designed to answer whether infants who initiated cART 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 cART (initiation driven by CDC stage and CD4 status), immediate cART with interruption after 40 weeks, or immediate cART with interruption after 96 weeks.[7,8] While the 2 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 cART saved by most children merits the potential risks associated with cessation.

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

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Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection (Last updated February 12, 2014; last reviewed February 12, 2014)

Panel's Recommendations

- Evaluation of plasma concentrations of antiretroviral drugs are not required in the management of most pediatric patients with HIV, but should be considered in children on combination antiretroviral therapy in the following scenarios: **(BII)**
  - Use of antiretroviral drugs with limited pharmacokinetic data and therapeutic experience in children (e.g., for use of efavirenz in children aged <3 years and darunavir with once-daily dosing in children aged <12 years);
  - Significant drug-drug interactions and food-drug interactions;
  - Unexpected suboptimal treatment response (e.g., lack of virologic suppression with history of medical adherence and lack of resistance mutations);
  - Suspected suboptimal absorption of the drug; or
  - Suspected dose-dependent toxicity.
- Evaluation of the genetic G516T polymorphism of drug metabolizing enzyme cytochrome P450 (CYP450) 2B6 in combination with the evaluation of plasma efavirenz concentrations is recommended for children aged <3 years receiving efavirenz due to significant association of this polymorphism with efavirenz concentrations **(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 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. A limited number of adult studies suggest that modified doses and regimen choices based on TDM result in achievement of targeted ARV drug concentrations and are associated with improved clinical response and/or tolerability.[1-9] In children, the usefulness of TDM to guide dosing of ARV drugs has been demonstrated in a limited number of non-randomized clinical trials and case reports.[6,7,10-17]

Dosing of ARV drugs in HIV-infected children and adolescents depends on chronological age and/or body parameters (e.g., height, weight). Ongoing growth requires continuous reassessment of dosing of ARV drugs in order to avoid low drug exposure and development of viral resistance and virologic failure. Developmental differences in drug absorption, distribution, metabolism, and elimination contribute to high variability and a greater frequency of suboptimal exposure to multiple therapeutic agents in children and adolescents compared to adults.[18] Suboptimal exposure to selected ARV agents with recommended dosing has been demonstrated in pediatric patients, especially in young children.[14,15,19-21]

Because of the diverse developmental challenges in palatability and acceptability of combination antiretroviral therapy (cART), children and adolescents are frequently faced with the use of altered dosing regimens and ARV combinations for which safety and efficacy have not been established in large clinical trials. Furthermore, dosing recommendations for ARV drugs at the time of licensing for pediatric use are frequently derived from a limited number of patients and pharmacokinetic (PK) modeling and may be revised as newer PK data become available.[14,15,19,21] The Panel recommends considering TDM for certain ARV agents when the newly approved pediatric formulation and/or dosing are used based on limited PK and efficacy data in small populations (see specific drug information sections). TDM can also be considered in management of treatment failure for children on cART to increase efficacy and to decrease toxicity.

Use of TDM to Improve Efficacy

The relationship between ARV drug concentrations and ARV efficacy must be clearly defined for TDM to be useful.[22-25] This association has been shown to be the strongest for protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) as well as for the CCR5 receptor antagonist maraviroc.[26-28] For nucleoside reverse transcriptase inhibitors (NRTIs), intracellular concentrations of their triphosphate metabolites have been shown to be most important in determining therapeutic response. Obtaining intracellular NRTI metabolite concentrations is expensive, labor-intensive, requires large blood volumes, and is limited to research settings. Limited data have demonstrated that serum concentrations of NRTIs are also correlated with virologic suppression; however, no efficacy plasma concentrations have been derived for NRTIs.[29]

Based on data from adult studies, consensus target efficacy plasma trough concentrations for treatment-naive and treatment-experienced patients have been developed by clinical pharmacology experts from the United States and Europe for the many PIs and NNRTIs, as well as the CCR5 receptor antagonist maraviroc (see Table 16). Efficacy trough concentrations for maraviroc and tipranavir have been derived in patients with multiple drug-resistant HIV strains only. Although exposure-response data for the PI darunavir, the NNRTI etravirine, and the integrase inhibitor raltegravir are accumulating, they have been considered insufficient to define target efficacy concentrations at this time.[30-33] Table 16 includes data on the plasma trough concentrations derived from clinical trials of these drugs.

Table 16. Target Trough Concentrations of Antiretroviral Drugs[a]

Drug	Concentration (ng/mL)
Established Efficacy Plasma Trough Concentrations	
Atazanavir	150
Fosamprenavir	400[b]
Indinavir	100
Lopinavir	1,000
Nelfinavir[c]	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Maraviroc	>50[d]
Tipranavir	20,500[d]
Plasma Trough Concentrations from Clinical Trials	
Darunavir[e]	3300 (1,255–7,368)[f]
Etravirine	275 (81–2,980)[f]
Raltegravir	72 (29–118)[f]

[a] Adapted from: *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

[b] Measurable amprenavir concentration

[c] Measurable active (M8) metabolite

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

[e] Darunavir dose 600 mg twice daily

[f] Median (range)

The suggested efficacy plasma trough concentrations are generally applicable to patients whose HIV is susceptible to the particular ARV drug. In treatment-experienced patients with virologic failure, a higher plasma trough concentration may be required to suppress viral replication when there is decreased susceptibility to the ARV drug.[11,34-36] For the majority of PIs, viral resistance develops cumulatively with successive mutations, and higher drug exposure can potentially overcome lower levels of resistance. The concept of inhibitory quotient (IQ) has been developed and successfully applied to certain PIs, such as lopinavir/ritonavir.[37] IQ is expressed as the ratio of patient plasma trough concentration (C_{min}) to specific viral susceptibility parameters (e.g., fold change in inhibitory concentration or the number of the drug specific resistance-associated mutations).[1,34] This approach does not apply to drugs with low, single mutation thresholds for resistance (e.g., the NNRTIs nevirapine and efavirenz) because it is not possible to overcome such resistance by increasing the ARV drug exposure. Suboptimal plasma concentrations of efavirenz and nevirapine have been linked to virologic failure in children.[10,21,38] Evaluation of efavirenz plasma concentrations in combination with pharmacogenetic evaluation for the polymorphism of the main drug metabolizing enzyme cytochrome P (CYP) 450 CYP2B6 is recommended if efavirenz is used in children aged <3 years to avoid suboptimal drug exposure (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

Use of TDM to Decrease Toxicity

The exposure-toxicity response relationship has been well defined for the PIs indinavir and atazanavir and the NNRTI efavirenz.[24,39] Increased frequency of indinavir-associated nephrolithiasis has been reported to be associated with elevated peak and trough plasma concentrations of the drug in adults (indinavir is not recommended for use in pediatric patients).[40] Increased plasma concentrations of atazanavir have been linked to elevated bilirubin concentrations in adolescents, and measurement of the atazanavir plasma concentrations has been suggested for management of the atazanavir-associated hyperbilirubinemia in adolescents.[39]

Adverse central nervous system (CNS) effects (e.g., CNS depression, dizziness, insomnia, hallucinations) associated with efavirenz have been shown to correlate with efavirenz plasma trough concentrations >4 mcg/mL in adult and pediatric studies.[10,41,42] TDM-guided reduction in the efavirenz dose has been shown to successfully reduce neuropsychiatric side effects while allowing for continued virologic suppression in a prospective open-label multicenter adult study.[43] A recent report on the PK of efavirenz in children aged <3 years demonstrated a significant relationship between high plasma efavirenz median concentrations and area under the curve versus time concentration (AUC) and drug-associated hematologic and CNS toxicity.[12] Evaluation of the efavirenz plasma concentrations in combination with determination of polymorphism of the main drug-metabolizing enzyme CYP2B6 should be considered for preventing and decreasing efavirenz associated adverse events in children aged <3 years (see next section on pharmacogenetics).

Pharmacogenetic Evaluation as Part of TDM

The pharmacogenetics of HIV therapy investigate the interactions between human genetic polymorphisms and PK and the outcome of cART. Multiple metabolizing and drug transporter genes have been studied for their association with efficacy and toxicity of antiretroviral drugs. The most clinically significant relationship is demonstrated by the association between the CYP2B6 G to T polymorphism and the PK, toxicity and the clinical response to efavirenz. CYP2B6 T516T and G516T genotypes have been associated with elevated plasma efavirenz concentrations and CNS toxicity in children and adults, while CYP2B6 G516G genotype has been linked to the low plasma concentrations of efavirenz, decreased rates of virologic suppression and development of resistance.[12,42,44,45] Adjustment of efavirenz dose based on a patient's CYP2B6 G516T genotype has been shown to minimize risk of development of resistance and treatment failure and avoid or decrease drug-associated toxicity in adults and adolescents.[11,46-48]

The effect of CYP2B6 G516T polymorphism on the PK of efavirenz appears to be most pronounced in younger children undergoing maturation of CYP450 enzymatic system.[38] In ongoing PACTG P1070 study, efavirenz dosing of approximately 40 mg/kg in children aged <3 years produced therapeutic efavirenz plasma concentrations in 68% of children with GG/GT 516 rapid CYP2B6 genotypes, while the same dose led to significantly higher exposure with treatment-related toxicities ≥grade 3 in children with TT 516 CYP2B6 genotype.[12] In this ongoing study, genotyping for CYP2B6 G516T polymorphism is incorporated in the pretreatment evaluation and will be used to determine the dosing regimen. While efavirenz is not recommended for initial therapy in children aged <3 years, should efavirenz use be considered in children aged <3 years, the Panel recommends obtaining CYP2B6 genotype as part of pretreatment evaluation and dose selection (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

Practical Considerations

The use of TDM in clinical practice poses multiple challenges, including availability of the ARV drug assays and certified laboratories; difficulties in collecting timed blood samples in children to obtain true plasma trough concentrations; prolonged time to obtain the results; limited availability of pharmacologic pediatric expertise; and cost and reimbursement considerations. More extended PK evaluation of the AUC in children involves higher volumes of blood samples, cost, and time commitment. Limited information on safety and effectiveness of dose adjustment strategies in children and adolescents may also limit the application of TDM in clinical practice.

When obtaining plasma concentrations in pediatric and adolescent patients, several important steps need to be taken. Crucially important for interpretation of the results is documentation of the following:

- Accurate information about the dose and formulation
- List of concomitant medications
- Food intake with the dose
- Timing of the dose and blood sample collection
- Adherence and resistance information

Additional practical suggestions on TDM of ARV drugs can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee[22] and several pediatric review manuscripts.[7,16,49] Most importantly, consultation with an expert in pediatric HIV pharmacology is required 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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Antiretroviral Drug-Resistance Testing (Last updated February 12, 2014; last reviewed February 12, 2014)

Panel's Recommendations
• Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment-naive patients **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**. • ARV drug resistance testing is recommended before changing therapy because of treatment failure **(AI*)**. • Resistance testing in patients with virological failure should be done while they are still on the failing regimen or within 4 weeks of discontinuation **(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 ARV therapy regimens **(BIII)**. • The absence of detectable resistance to a drug does not ensure that use of the drug will be successful. Consequently, previously used ARV agents and previous resistance test results must be reviewed when making decisions regarding the choice of new agents for patients with virologic failure **(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*)**. • Consultation with a pediatric HIV specialist is recommended for interpretation of resistance assays when considering starting or changing an ARV regimen in pediatric patients **(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*

HIV Drug-Resistance and Resistance Assays

HIV replication is a continuous process in most untreated patients, leading to the daily production of billions of virions. The goal of combination antiretroviral therapy (cART) is to suppress HIV replication as rapidly and fully as possible, as indicated by a reduction in plasma HIV RNA to below the limit of detection of the most sensitive assays available. Unfortunately, mutations in HIV RNA arise during viral replication because HIV reverse transcriptase (RT) is a highly error-prone enzyme. Consequently, ongoing replication in the presence of antiretroviral (ARV) drugs, as occurs in suboptimal adherence, readily and progressively selects for strains of HIV with mutations that confer drug resistance. Viruses harboring resistance-associated mutations can be transmitted in both perinatal and non-perinatal infection, underscoring the importance of resistance testing at the time of HIV diagnosis before cART initiation.[1,2]

Drug-resistance detection methods vary depending on the class of ARV agents. Viral coreceptor (tropism) assays are used to detect virus with tropism that will (CCR5 tropism) or will not (CXCR4 tropism or dual/mixed [D/M] tropism) be blocked by CCR5 antagonists. Detection of virus with CXCR4 or D/M tropism indicates resistance to CCR5 antagonists. Both genotypic assays and phenotypic assays currently are used to detect the presence of virus that is resistant to inhibitors of the HIV reverse transcriptase (RT), integrase (IN), or protease (PR) enzymes. Clinical experience with testing for viral resistance to other agents is more limited, but genotypic assays that assess mutations in gp41 (envelope) genes also are commercially available. Experience is also limited with the use of commercially available genotypic and phenotypic assays in the evaluation of drug resistance in patients infected with non-B subtypes of HIV.[3,4] Table 17 summarizes the indications for using available resistance testing.

Genotypic Assays

Genotypic assays for resistance to RT and PR inhibitors and IN strand transfer inhibitors are based on polymerase chain reaction (PCR) amplification and analysis of the RT, PR, and IN coding sequences present in HIV RNA extracted from plasma. Genotypic assays can detect resistance mutations in plasma samples containing approximately 1,000 copies/mL or more of HIV RNA and results generally are available within 1 to 2 weeks of sample collection.[5] Not all available genotypic tests include IN resistance; it may need to be specifically requested. Interpretation of test results requires knowledge of the mutations selected by different ARV drugs and of the potential for cross resistance to other drugs conferred by certain mutations. For some drugs, the genetic barrier to the development of resistance is low and a single nucleotide mutation is enough to confer high-level resistance sufficient to remove any clinical utility of the drug. This is exemplified by resistance to nevirapine and efavirenz resulting from mutations in the HIV RT (e.g., K103N). Other mutations lead to drug resistance but simultaneously impair HIV replication. Clinically useful activity of the ARV agent may therefore remain, as demonstrated by evidence of continued clinical benefit from lamivudine in individuals with evidence of the high-level lamivudine resistance engendered by the M184V RT mutation.[6] By contrast, HIV evolution to high-level resistance to some drugs is associated with the emergence of mutations that confer resistance as well as compensatory mutations that allow the virus to replicate more efficiently in the presence of the ARV agent. In addition, polymorphisms that occur naturally or in the presence of drug and are not significant alone may confer clinically significant drug resistance when present with other polymorphisms or major resistance mutations.[7]

The International AIDS Society-USA (IAS-USA) and the Stanford University HIV Drug Resistance Database maintain lists of resistance mutations that confer resistance to currently available ARV drugs (see http://www.iasusa.org/resistance_mutations, or http://hivdb.stanford.edu). A variety of online tools analyze the simultaneous effect of all mutations detected in a patient in order to assist the provider in interpreting genotypic test results. Although the response to cART in children and adolescents is not always predicted by the results of genotypic resistance assays, clinical trials in adults have demonstrated the benefit of resistance testing combined with consultation with specialists in HIV drug resistance in improving virologic outcomes.[5,8-14] Given the potential complexity of interpretation of genotypic resistance, it is recommended that clinicians consult with a pediatric HIV specialist for assistance in the interpretation of genotypic results and design of an optimal new regimen.

Phenotypic Assays

Phenotypic resistance assays provide a more direct assessment of the impact on viral replication of mutations that are present in an individual's HIV variants. As they are most often performed, phenotypic assays involve PCR amplification of the predominant RT, IN, PR, or gp41 envelope gene sequences from patient plasma and insertion of those amplified patient sequences into the backbone of a cloned strain of HIV that expresses a reporter gene. Replication of this recombinant virus in the presence of a range of drug concentrations is monitored by quantification of the reporter gene and is compared with replication of a reference drug susceptible HIV variant. The drug concentration that inhibits viral replication by 50% (i.e., the mean inhibitory concentration, or IC_{50}) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance change). Automated, recombinant phenotypic assays that can produce results in 2 to 3 weeks are commercially available; however, they are more costly than genotypic assays.

Analytic techniques have also been developed to use the genotype to predict the likelihood of a drug-resistant phenotype. This bioinformatic approach, currently applicable for RT, IN, and PR inhibitor resistance only, matches the pattern of mutations obtained from the patient sample with a large database of samples for which both genotype and phenotype are known. Therefore, the sample is assigned a predicted phenotype susceptibility (or virtual phenotype) based on the data from specimens matching the patient's genotype.

Tropism (Viral Coreceptor Usage) Assays

HIV enters cells by a complex, multistep process that involves sequential interactions between the HIV envelope protein molecules and the CD4 T lymphocyte (CD4) receptor, and then with either the CCR5 or CXCR4 coreceptor molecules, culminating in the fusion of the viral and cellular membranes. Viruses initially are CCR5 tropic in the majority of untreated individuals, including infants and children perinatally infected with HIV. However, a shift in coreceptor tropism often occurs over time, from CCR5 usage to either CXCR4- or D/M-tropic. ARV-treated patients with extensive drug resistance are more likely to harbor detectable CXCR4- or D/M-tropic virus than untreated patients with comparable CD4 counts.[15-17]

Resistance to CCR5 antagonists is detected using specialized phenotypic assays (Phenoscript [VIRalliance] and Trofile [Monogram Biosciences, Inc]). These assays involve the generation of recombinant viruses bearing patient-derived envelope proteins (gp120 and gp41). The relative capacity of these pseudoviruses to infect cells bearing the cell surface proteins CCR5 or CXCR4 is based on the expression of a reporter gene.

Detection of CXCR4 of D/M tropism is a contraindication to the use of the CCR5 antagonists as part of a therapeutic regimen. Coreceptor assays must be performed before a CCR5 inhibitor is used and should be considered in patients exhibiting virologic failure on a CCR5 inhibitor such as maraviroc.

The Trofile assay takes about 2 weeks to perform and requires a plasma viral load ≥1,000 copies/mL and at least 3 mL of plasma. The initial version of the Trofile assay used during the clinical trials that led to the licensure of maraviroc was able to detect CXCR4-tropic virus with 100% sensitivity when present at a frequency of 10% of the plasma virus population, but only 83% sensitivity when the variant was present at a frequency of 5%. In initial clinical trials of CCR5 antagonist drugs, this sensitivity threshold was not always sufficient to exclude the presence of clinically meaningful levels of CXCR4- or D/M-tropic virus in patients initiating a CCR5 inhibitor-based regimen. The current enhanced sensitivity version of the TrofileTM assay (Trofile-ES™) is able to detect CXCR4- or D/M-tropic virus representing as little as 0.3% of the plasma virus.[18,19]

One of the tropism assays can also be performed following amplification of HIV sequences from peripheral blood DNA (Trofile-DNA™ [Monogram Biosciences, Inc.]) and may be most useful when a change to a regimen containing a CCR5 antagonist is being considered for individuals with plasma viral load below 1,000 copies/mL and can be used even when the viral load is undetectable (e.g., if single-drug substitution for toxicity).

Limitations of Current Resistance and Tropism Assays

Limitations of the genotypic, phenotypic, and phenotype-prediction assay approaches include lack of uniform quality assurance testing and high cost. In addition, drug-resistant variants are likely to exist at low levels in every HIV-infected patient. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population or are present in the reservoir of latently infected cells may not be detected by any of the currently available commercial resistance assays.[20] A comprehensive review of the past use of ARV agents and the virologic responses to those agents, and all prior resistance mutations (i.e., cumulative genotype), even if not present on the current genotype, is important in making decisions regarding the choice of new agents for patients with virologic failure.[21]

The primary limitations of phenotypic assays are that their predictive power depends upon the sensitivity of the genotypic methods used and the number of matches to the patient's genotype. These tests also are more costly than genotypic testing, therefore, their use should be reserved for clinical settings in which the information they provide will add benefit (see Table 17).

Genotypic assays to assess tropism have been proposed as an alternative approach to detemining the tropism of plasma HIV. However, they are not currently recommended because the limited experience with this approach indicates that the sensitivity may be lower than phenotypic tropism assays, particularly in the setting of CCR5 antagonist interruption where reversion to wild-type may occur.[22,23]

Although drug resistance may be detected in the circulating plasma of infants, children, and adults who are not receiving therapy at the time of the assay, loss of detectable resistance and reversion to predominantly wild-type virus often occur in the first 4 to 6 weeks after ARV drugs are stopped.[24-26] As a result, resistance testing is of greatest value when performed prior to or within 4 weeks after drugs are discontinued, or as soon after diagnosis as possible.[27] The absence of detectable resistance to a drug at the time of testing does not ensure that future use of the drug will be successful,[1,28] especially if the agent shares cross resistance with drugs previously used. It may be prudent to repeat resistance testing if an incomplete virological response to a new treatment regimen is observed in an individual with prior treatment failure(s) (see Management of Children Receiving Antiretroviral Therapy).

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant strains to newly infected individuals (via perinatal and non-perinatal transmission of HIV) has been well documented and is associated with suboptimal virologic response to initial cART if this resistance is not taken into account when designing the initial regimen.[29-33] Drug-resistant variants of HIV may persist for months after birth in infected infants[34] and impair the response to cART.[35] Consequently, ARV drug-resistance testing is recommended for all treatment-naive children before therapy is initiated. Standard genotypic testing is preferred in this setting because it may reveal the presence of both RT and PR resistance mutations and polymorphisms that facilitate the replication of drug-resistant virus. Genotypic testing for integrase resistance mutations prior to initial treatment is only recommended in special circumstances (e.g., acquisition of HIV from an individual treated with an integrase inhibitor with concern for transmission of integrase resistance).

Use of Resistance Assays in the Event of Virologic Failure

Several studies in adults[5,8-14] have indicated that early virologic responses to salvage regimens were improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Although not yet confirmed in children,[36] resistance testing appears to be a useful tool in selecting active drugs when changing ARV regimens in cases of virologic failure. Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction because virologic failure in the setting of cART may be associated with resistance to only one component of the regimen.[3] Poor adherence should be suspected when no evidence of resistance to a failing regimen is identified (see Management of Children Receiving Antiretroviral Therapy).

Table 17: Recommendations for Use of Available Resistance Testing

Resistance Test	Initial Treatment	Virologic Failure
Standard genotype (RT, PR)	Resistance testing indicated	Resistance testing indicated
Integrase phenotype/genotype	Only if concern for acquisition of virus with resistance	If failure on integrase inhibitor
Trofile™	Only if considering CCR5 antagonist as part of initial treatment	Only if considering CCR5 antagonist for subsequent regimen
Phenotype (RT, PR)	Not recommended prior to initial treatment unless genotypic evidence that multi-drug resistance was acquired	In the setting of extensive drug resistance, may assist in determining most active cART regimen. Must be used in conjunction with cumulative genotypic resistance results and cART history and response

Key to Acronyms: cART = combination antiretroviral therapy; PR = protease; RT = reverse transcriptase

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Conclusion (Last updated February 12, 2014; last reviewed February 12, 2014)

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral (ARV) drugs and newer classes of drugs are approved. 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 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, 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 of the Infectious Disease Society of America, the Pediatric Infectious Disease 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)

Abacavir (ABC, Ziagen) (Last updated February 12, 2014; last reviewed February 12, 2014)

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 (FDC) Tablets

With Lamivudine (3TC):

- ABC 600 mg + 3TC 300 mg (Epzicom)

With Zidovudine (ZDV) and 3TC:

- ABC 300 mg + ZDV 300 mg + 3TC 150 mg (Trizivir)

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) twice daily.

Weight Band Dosing (Weight ≥14 kg)

Scored 300-mg tablet.

Weight (kg)	Twice-Daily Dosage Regimen		
	AM Dose	PM Dose	Total Daily Dose
14 to 21 kg	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte (CD4) counts for more than 24 weeks, changing from twice-daily to once-daily dosing at 16–20 mg/kg/day to a maximum of 600 mg once daily is recommended if part of a once-daily regimen (see text below).

Adolescent (Aged ≥16 Years)/Adult Dose:

- 300 mg twice daily or 600 mg once daily.

Trizivir

Adolescent (Weight ≥40 kg)/Adult Dose:

- One tablet twice daily.

Selected Adverse Events

- Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough and shortness of breath).
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; 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 ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.
- Warn patients and parents about risk of serious potentially fatal HSR. Occurrence of HSRs requires **immediate and permanent discontinuation** of ABC. Do not re-challenge.
- ABC can be given without regard to food. Oral solution does not require refrigeration.

Metabolism

- Systemically metabolized by alcohol dehydrogenase and glucuronyl transferase

Epzicom

Adolescent (Aged ≥16 Years)/Adult Dose:

- One tablet once daily.

- Intracellularly metabolized to carbovir triphosphate (CBV-TP).
- Active metabolite is 82% renally excreted.
- ABC requires dosage adjustment in hepatic insufficiency.
- Do not use fixed-dose combinations such as Trizivir and Epzicom in patients with impaired hepatic function because the dose of abacavir cannot be adjusted.
- Do not use Trizivir and Epzicom 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.)

- 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 below under Pediatric Use).
- Through interference with alcohol dehydrogenase and glucuronyl transferase, alcohol increases abacavir levels by 41%.

Major Toxicities

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. HSR to abacavir is a multi-organ clinical syndrome usually characterized by rash or signs or symptoms in two or more of the following groups:
  - Fever
  - Constitutional, including malaise, fatigue, or achiness
  - Gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain
  - Respiratory, including dyspnea, cough, or pharyngitis.
- Laboratory and radiologic abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have also been reported. Pancreatitis can occur. This reaction generally occurs in the first 6 weeks of therapy, but has also been reported after a single dose. If an HSR is suspected, abacavir should be stopped **immediately and not restarted—hypotension and death may occur upon re-challenge**. The risk of abacavir HSR is associated with the presence of HLA-B*5701 allele; it is greatly reduced by testing patients for HLA-B*5701 prior to the initiation of therapy and by not using abacavir in those who test positive for the HLA-B*5701.
- *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.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ABC.html).

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.

Efficacy

Abacavir used either twice daily or once daily has demonstrated durable antiviral effectiveness in pediatric trials.[1-3]

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 and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure.[4,5] 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] Intracellular concentrations of NRTIs are most strongly associated with antiviral effectiveness, and the active form of abacavir is the intracellular metabolite carbovir triphosphate (CBV-TP).[9,10] 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.[11] Intracellular CBV-TP concentrations are affected by gender and have been reported to be higher in females than in males.[11-13] This effect of gender and the interactions with PIs (see Drug Interactions section below) on abacavir PK further complicate linking 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 boosted PIs atazanavir/ritonavir and lopinavir/ritonavir, respectively.[14] In a study comparing PK parameters of abacavir in combination with either lopinavir/ritonavir or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of lopinavir/ritonavir; however, the CBV-TP concentrations appeared to be increased in the lopinavir/ritonavir cohort.[13] The mechanism and the clinical significance of these drug interactions with the PIs are unclear. No dose adjustment for abacavir or PIs is recommended.

Dosing

Frequency of Administration

Abacavir 600 mg is administered once daily in adults; however, once-daily use in children remains controversial. The PENTA-13 crossover trial compared abacavir exposure at 16 mg/kg once daily with 8 mg/kg twice daily in 24 children aged 2 to 13 years who had undetectable or low, stable viral loads. This study showed equivalent AUC_{0-24} for both dosing regimens and improved acceptability of therapy in the once-daily dosing arm.[15,16] However, trough abacavir plasma concentrations were lower in younger children (aged 2–6 years) receiving the once-daily regimen.[16] The PENTA-15 crossover trial studied 18 children aged 3 to 36 months, again comparing abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in children with viral loads <400 copies/mL or with stable viral loads on twice-daily abacavir at baseline. ABC $AUC_{0\text{-}24}$ and clearance were similar in children on the once- and twice-daily regimens. After the change from twice-daily to once-daily abacavir, viral load remained <400 copies/mL in 16 of 18 participants through 48 weeks of monitoring.[17] A study of 41 children (aged 3 to 12 years in Uganda who were stable on twice-daily fixed-dose co-formulation of abacavir/lamivudine) also showed equivalent $AUC_{0\text{-}24}$ and stable clinical outcome (i.e., disease stage and CD4 T lymphocyte [CD4] cell count) after the switch to once-daily abacavir during a median follow-up of 1.15 years. Virologic outcome was not evaluated in this study.[18]

Abacavir Steady-State Pharmacokinetics with Once-Daily or Twice-Daily Dosing

Study (Reference)	Pediatric PENTA 15[17]		Pediatric PENTA 13[16]		Pediatric Arrow[18]		Adult[6]		Adult[11]	
Location	Europe		Europe		Uganda		United States		United States	
N of Subjects	18		14		36		15	15	27	
Mean Age Years	2		5		7		16	22	45	
Sex % Male	56%		43%		42%		53%	53%	70%	
Body Weight kg	11		19		19		63[a]	72[a]	N/A	
Subjects Using PI(s)	8		1		0		9	0	N/A	
Dosing Interval Hours	12	24	12	24	12	24	12	12	12	24
Dose mg	8[a]	16[a]	8[a]	16[a]	19[b]	19[b]	300	300	300	600
Dose Range mg/kg	7.7–8.3[c]	15.5–16.3[c]	5.0–8.4	15.6–17.1	15.4–23.1[c]	14.6–23.1	N/A	N/A	N/A	N/A
$AUC_{0\text{-}24}$ mg*hr/L	10.85[d]	11.57[b]	9.91[d]	13.37[b]	15.6[b]	15.28[b]	7.01	6.59	7.90[d]	8.52[d]
C_{max} mg/L	1.38[d]	4.68[d]	2.14[d]	4.80[d]	4.18[d]	6.84[d]	2.58	2.74	1.84[d]	3.85[d]
C_{min} mg/L	0.03[d]	<0.02[d]	0.025[d]	<0.015[d]	0.02[d]	0.016[d]	N/A	N/A	N/A	N/A
Cl/F/kg L/hr/kg	1.47[d]	1.38[d]	1.58[d]	1.16[d]	1.23[d]	1.24[d]	9.80[e]	12.10[e]	N/A	N/A

Data are medians except as noted.

[a] mg/kg

[b] total daily dose in mg/kg (divided doses were given but sometimes in unequal amounts morning and evening)

[c] interquartile range

[d] geometric mean

[e] mL/min/kg

Key to Acronyms: AUC = area under the curve; C_{max} = maximal (peak) concentration; C_{min} = minimal (trough) concentration; PI = protease inhibitor

Most recently, a pediatric PK model was developed based on data from 69 children in the PENTA trials (13 and 15) and ARROW study.[19] Irrespective of age, body weight was identified as the most significant factor influencing the oral clearance of abacavir in children. Predicted 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 showed that equivalent systemic plasma abacavir exposure was achieved after once- or twice-daily dosing regimens. The model did not include information on ethnicity and other potentially important demographic factors. No clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir. None of the pediatric clinical trials evaluated the pharmacodynamically most important intracellular CBV-TP concentrations. All three pediatric studies presented in the table above enrolled only patients who had low viral loads or were clinically stable on twice-daily abacavir before changing to once-daily dosing. Recent 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] Therefore, as part of a once-daily regimen, the Panel suggests a switch from twice-daily to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose [maximum of 600 mg] once daily) for clinically stable patients with undetectable viral loads and stable CD4 cell counts for more than 6 months.

Toxicity

Abacavir has less of an effect on mitochondrial function than zidovudine, stavudine, or didanosine.[1,2]

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Didanosine (ddI, Videx) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

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: 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Neonate/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 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 aged 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
- Electrolyte abnormalities
- 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 in adults when didanosine is used in combination with tenofovir 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 oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of didanosine than for the enteric-coated formulation.

Adolescent/Adult Dose

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

Didanosine in Combination with Tenofovir Disoproxil Fumarate (Tenofovir):

- This combination should be avoided, if possible, because of enhanced didanosine toxicity.

Pediatric/Adolescent Dose of Didanosine when Combined with Tenofovir:

- 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 Tenofovir

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

- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.

Metabolism

- 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)

- *Absorption:* The presence of antacids in didanosine oral solution 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 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 be used unless the potential benefit clearly outweighs the potential risk (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 severe hepatomegaly with steatosis, including fatal cases, have been reported, and are more common with didanosine in combination with stavudine. Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir or stavudine) can occur. Increased liver enzymes and retinal depigmentation and optic neuritis have been reported.

- *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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/didanosine.html).

Pediatric Use

Approval

Didanosine is Food and Drug Administration (FDA)-approved for use in children as part of a dual-nucleoside reverse transcriptase inhibitor backbone in combination antiretroviral therapy.

Dosing

Standard Dose in Children

Recommended doses of didanosine oral solution in children have traditionally been 90 to 150 mg/m^2 body surface area per dose twice daily. Doses higher than 180 mg/m^2 body surface area twice daily are associated with increased toxicity.[1] The pharmacokinetic (PK) variable of greatest pharmacodynamic significance is the area under the curve (AUC), with virologic response best with didanosine AUC ≥0.60 mg*h/L.[2,3] In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg/m^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with adequate exposure predicted in 88% of patients at a dose of 120 mg/m^2 body surface area twice daily,[3] so that is the currently recommended dose for children aged 8 months to 3 years.

Special Considerations in Ages 2 Weeks to <3 Months

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m^2 body surface area per dose twice daily, increasing to 120 mg/m^2 body surface area per dose twice daily at age 8 months. However, 2 small studies suggest that a higher AUC is seen in infants aged <6 weeks and that a dose of 100 mg/m^2 body surface area per day (either as 50 mg/m^2 body surface area per dose twice daily or 100 mg/m^2 body surface area once daily) in infants aged <6 weeks achieves AUCs consistent with those seen at higher doses when used in older children.[4,5] Therefore, because these PK differences in younger infants (aged 2 weeks–3 months) compared with older children raise concern for increased toxicity in the younger age group, the Panel recommends a dose of 50 mg/m^2 of body surface area twice daily for infants aged younger than 3 months.

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. In a study of 10 children aged 4 to 10 years, EC didanosine (Videx EC) administered as a single dose of 240 mg/m^2 body surface area once daily was shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine.[4] The resultant intracellular (active) drug concentrations are unknown. In 24 HIV-infected children, didanosine oral solution at a dose of 180 mg/m^2 body surface area once daily was compared with 90 mg/m^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group.[6] Long-term virologic suppression with a once-daily regimen of efavirenz, emtricitabine, and didanosine (oral solution or EC beadlet capsules) was reported in 37 treatment-naive children aged 3 to 21 years.[7] The didanosine dose used in that study was 240 mg/m^2/dose once daily, and PK analysis showed no dose changes were needed to reach PK targets.[7] A European trial of once-daily combination therapy in 36 children aged 3 to 11 years that included didanosine at a dose of 200 to 240 mg/m^2 body surface area demonstrated safety and efficacy with up to 96 weeks of follow up.[8] In 53 children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg/m^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was less in the children given once-daily therapy.[9] In 51 children (median age 6.0 years, range 2.5 to 15.0 years) in Burkina Faso, the once-daily combination of didanosine-lamivudine-efavirenz resulted in Week-48 viral load <300 copies/mL in 81% of treated participants. That study used didanosine at a dose of 240 mg/m^2/day, administered in the fasting state as tablets with a separate antacid (not enteric-coated capsules).[2]

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 regardless of whether didanosine oral solution was given to children with or without food, systemic exposure measured by AUC was similar; absorption of didanosine administered with food was slower and elimination more prolonged.[10] 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.[11,12] 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.[13]

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Emtricitabine (FTC, Emtriva) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Combination Tablets:

- With tenofovir disoproxil fumarate (tenofovir): 200 mg emtricitabine plus 300 mg tenofovir (Truvada)
- With tenofovir and efavirenz : 200 mg emtricitabine plus 300 mg tenofovir plus 600 mg efavirenz (Atripla)
- With tenofovir and rilpivirine: 200 mg emtricitabine plus 300 mg tenofovir plus 25 mg rilpivirine (Complera)
- With emtricitabine and elvitegravir and cobicistat: 200 mg emtricitabine plus 150 mg elvitegravir plus 150 mg cobicistat plus 300 mg tenofovir (Stribild)

Dosing Recommendations

Neonate/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 (for Children who Weigh >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 (Aged ≥12 Years And ≥35 Kg and Adult Dose:

- 1 tablet once daily.

Atripla

Adolescent (Aged ≥12 Years And ≥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 (HBV)-coinfected patients who discontinue emtricitabine
- Hyperpigmentation/skin discoloration on palms and/or soles

Special Instructions

- Emtricitabine can be given without regard to food; however, administer Atripla on an empty stomach because it also contains efavirenz.
- Emtricitabine oral solution can be kept at room temperature up to 77°F (25°C) if used within 3 months; refrigerate for longer-term storage.
- Before using emtricitabine, screen patients for HBV.

Metabolism

- 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

- See efavirenz section for pregnancy warning.

Complera

Adult Dose (Aged ≥18 Years):

- 1 tablet once daily in treatment-naive adults with baseline plasma RNA <100,000 copies/mL.
- Administer with food.

Stribild

Adult Dose (Aged ≥18 Years):

- 1 tablet once daily in treatment-naive adults.
- Administer with food.

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.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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):* 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-coinfected patients who changed from emtricitabine-containing to non-emtricitabine-containing regimens.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/FTC.html).

Pediatric Use

Approval

Emtricitabine is Food and Drug Administration (FDA)-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-NRTI 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 to 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*ug/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 hepatitis B. For a comprehensive review of this topic, hepatitis C, and tuberculosis during HIV co-infection, please see the Pediatric Opportunistic Infections Guidelines.

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Lamivudine (3TC/Epivir) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

Oral Solution: 10 mg/mL (Epivir), 5 mg/mL (Epivir HBV[a])

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

Combination Tablets:

With Zidovudine:

- 150 mg 3TC plus 300 mg zidovudine (generic and Combivir)

With Abacavir:

- 300 mg 3TC plus 600 mg abacavir (Epzicom)

With Zidovudine and Abacavir:

- 150 mg 3TC plus 300 mg zidovudine plus 300 mg abacavir (Trizivir)

[a] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The strength of 3TC in Epivir HBV solution and tablet was maximized for treatment of hepatitis B virus (HBV) only. 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 3TC dose for treatment of HIV infection.

Dosing Recommendations

Neonate/Infant Dose (Aged <4 Weeks) for Prevention of Transmission or Treatment:

- 2 mg/kg twice daily

Pediatric Dose (Aged ≥4 Weeks):

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

Pediatric Dosing for Scored 150-mg Tablet (Weight ≥14 kg)

Weight	AM dose	PM Dose	Total Daily Dose
14 to 21kg	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30 kg	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30 kg	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (Aged ≥16 Years)/Adult Dose:

Body Weight <50 kg:

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

Body Weight ≥50 kg:

- 150 mg twice daily or 300 mg once daily

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic HBV infection

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before administering 3TC.

Metabolism

- Renal excretion—dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with creatinine clearance (CrCl) <50 mL/min, on dialysis, or with impaired hepatic function.

Combivir

Adolescent (Weight ≥30 kg)/Adult Dose:

- 1 tablet twice daily

Trizivir

Adolescent (Weight >40 kg)/Adult Dose:

- 1 tablet twice daily

Epzicom

Adolescent (Aged >16 Years and Weight >50 kg)/ Adult Dose:

- 1 tablet once daily

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

- *Renal elimination:* Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* 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, pancreatitis, 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/3TC.html).

Pediatric Use

Approval

Lamivudine is Food and Drug Administration (FDA)-approved for use in 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.[2-10] Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone.[3-5,7,9,10] 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 WHO 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 lower 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]

Dosing Considerations—Once Daily versus Twice Daily Administration

The standard adult dosage for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. Population PK data indicate that once-daily dosing of 8 mg/kg leads to area under the curve $(AUC)_{0\text{-}24}$ values similar to 4 mg/kg twice daily but C_{min} values significantly lower and C_{max} values significantly higher in children aged 1 to 18 years.[15] 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 3 to 36 months of age in the PENTA 15 trial.[16] Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. $AUC_{0\text{-}24}$ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent $AUC_{0\text{-}24}$ and good clinical outcome (disease stage and CD4 T lymphocyte [CD4] cell count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years.[17] 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 didanosine (ddI), 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.[18] 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 ddI, severe immunosuppression, and non-clade B virus. In addition, rates of virologic failure and resistance profiles were not separated by age. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged 3 years and older 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.

Table: Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine

Study/(Reference)	PENTA 15[24]		PENTA 13[2]		ARROW[25]	
Location	Europe		Europe		Uganda	
N	17		14		35	
Age (Years)	2		5		7	
Sex (% Male)	56%		43%		42%	
Race (% Black or African American)	78%		Not Reported		100%	
Body Weight (kg)	11		19		19	
Concurrent PI Use	8		1		0	
Dosing Interval (hours)	12	24	12	24	12	24
Administered Dose (mg/kg)	4.04	8.02	4.05	8.1	4.7	9.6
AUC_{0-24} (mg*hr/L)	9.48[a]	8.66[a]	8.88[a]	9.80[a]	11.97[a]	12.99[a]
C_{max} (mg/L)	1.05[a]	1.87[a]	1.11[a]	2.09[a]	1.80[a]	3.17[a]
C_{min} (mg/L)	0.08[a]	0.05[a]	0.067[a]	0.056[a]	0.08[a]	0.05[a]
Cl/F/kg (L/hr/kg)	0.79[a]	0.86[a]	0.90[a]	0.80[a]	0.79[a]	0.72[a]

[a] Geometric mean

Note: Data are medians except as noted.

Key to Acronyms: AUC = area under the curve; PI = protease inhibitor

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 in adolescents aged 16 and older who weigh 50 kg or more.[19,20]

WHO Dosing

Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150-mg scored tablets.[21,22]

Both emtricitabine and lamivudine have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection the reader should access the Pediatric Opportunistic Infections guidelines.

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Stavudine (d4T, Zerit) (Last updated February 12, 2014; last reviewed February 12, 2014)

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, 40 mg

Generic: Stavudine capsules and solution have been approved by the Food and Drug Administration for manufacture and distribution in the United States

Dosing Recommendations

Neonate/Infant Dose (Birth to 13 Days):

- 0.5 mg/kg twice daily

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

- 1 mg/kg twice daily

Adolescent (≥30 kg)/Adult Dose:

- 30 mg 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

- Renal excretion 50%. Decrease dose in renal dysfunction.

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

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other Nucleoside Reverse Transcriptase Inhibitors (NRTIs):* Stavudine should not be administered in combination with zidovudine because of virologic antagonism.
- *Overlapping toxicities:* The combination of stavudine and didanosine is not recommended for initial therapy 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 (cART), 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 those 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://www.iasusa.org/resistance_mutations/index.html), and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/d4T.html).

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 side 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 cART 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) 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 young children.[14]

Toxicity

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving cART.[15,16] In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest—but significantly higher—rate of clinical and laboratory toxicities than those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use.[16] Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults.[3,17] In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children.[16]

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.[18-21] There are concerns that children with metabolic disorders and abnormalities in body fat distribution including subcutaneous fat loss and central fat accumulation are potentially at increased risk of cardiovascular disease in early adulthood.[22,23] 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.[22-28] 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.[25] 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.[25,26] Improvements in lipodystrophy have been observed among Thai children after discontinuation of stavudine in two separate studies.[27,29] 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.[30-32] 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] The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available[33] (for additional information on lactic acidosis see Table 11g 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.[30,34-36] In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group 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 recommends that stavudine be phased out of use because of unacceptable toxicity, with a strong recommendation 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 2 doses: similar efficacy with either the 30-mg or 40-mg dose[40] but a significantly lower incidence of peripheral neuropathy in the 30-mg than in the 40-mg group, but the overall incidence 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 was 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 3910 adult patients initiated 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 and that patients receiving the higher dose were more likely to discontinue stavudine use (OR 1.71) during the first year on cART.[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 South Africa.[44]

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]

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, 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.[46]

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated February 12, 2014; last reviewed February 12, 2014)

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)

Tablet: 150 mg, 200 mg, 250 mg, and 300 mg

Combination Tablets:

With emtricitabine:

- 200 mg emtricitabine plus 300 mg tenofovir disoproxil fumarate (hereafter, tenofovir) (Truvada)

With emtricitabine plus efavirenz:

- 200 mg emtricitabine plus 600 mg efavirenz plus 300 mg tenofovir (Atripla)

With emtricitabine plus rilpivirine:

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

With emtricitabine plus elvitegravir plus cobicistat :

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

Dosing Recommendations

Neonate/Infant Dose:

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

Pediatric Dose (Aged ≥2 Years to <12 Years)*:

- 8 mg/kg/dose once daily

Oral Powder Dosing Table

Body Weight kg	Oral Powder Once Daily Scoops of Powder
10 to <12	2
12 to <14	2.5
14 to <17	3
17to <19	3.5
19 to <22	4
22 to <24	4.5
24 to <27	5
27 to <29	5.5
29 to <32	6
32 to <34	6.5
34 to <35	7
≥35	7.5

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density (BMD)

Special Instructions

- Oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg tenofovir.
- Mix oral powder in 2 to 4 ounces 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 oral powder with liquid: the powder may float on the top even after vigorous stirring.
- Tenofovir can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains efavirenz, the combination tablet should be administered on an empty stomach.

Tablet Dosing Table
(Aged ≥2 Years and Weight ≥17 kg)

Body Weight kg	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)* and Adult Dose:

- 300 mg once daily

Combination Tablets

Truvada (Tenofovir plus Emtricitabine):

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

Atripla (Tenofovir plus Emtricitabine plus Efavirenz):

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

Complera (Tenofovir plus Emtricitabine plus Rilpivirine):

- Adult dose (aged ≥18 years): 1 tablet once daily in treatment-naive adults with baseline viral load <100,000 copies/mL. Administer with a meal.

Stribild (Tenofovir plus Emtricitabine plus Elvitegravir plus Cobicistat):

- Adult dose (aged ≥18 years): 1 tablet once daily in treatment-naive adults. Administer with food.

Tenofovir In Combination With Didanosine:

- Co-administration increases didanosine concentrations, so the combination of tenofovir and didanosine should be avoided if possible. If used, requires didanosine dose reduction (see section on didanosine).

Tenofovir in Combination with Atazanavir:

- Co-administration reduces atazanavir concentrations, so when atazanavir is used in combination with tenofovir; atazanavir should always be boosted with ritonavir. Atazanavir co-administration increases tenofovir concentrations, so monitor for tenofovir toxicity.

Tenofovir in Combination with Ritonavir-Boosted Lopinavir/Ritonavir:

- Co-administration increases tenofovir concentrations. Monitor for tenofovir toxicity.

- Measure serum creatinine and urine dipstick for protein and glucose before starting a tenofovir-containing regimen and monitor serum creatinine and urine dipstick for protein and glucose at intervals during continued therapy. Measure serum phosphate if clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before use of tenofovir. Severe acute exacerbation of HBV infection can occur when tenofovir is discontinued; therefore, monitor hepatic function for several months after therapy with tenofovir is stopped.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Metabolism

- Renal excretion.
- Dosing of tenofovir 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.

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

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

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (tenofovir).
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is co-administered with tenofovir and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors (PIs):* Tenofovir decreases atazanavir plasma concentrations. Atazanavir without ritonavir should not be co-administered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-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):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density (BMD) have been reported in both adults and children taking tenofovir; 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.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/tenofovir.html).

Pediatric Use

Approval

Tenofovir is Food and Drug Administration (FDA)-approved for use in children aged ≥2 years when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

Efficacy in Clinical Trials in Adults Compared to Children and Adolescents

The standard adult dose of tenofovir 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 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 dose is highly effective.[2,3]

In children aged 12 to <18 years, no difference in viral load response was seen between 2 treatment groups in a randomized, placebo-controlled trial of tenofovir 300 mg once daily or placebo, plus an optimized background regimen, in 87 treatment-experienced adolescents in Brazil and Panama.[4-6] Subgroup analyses suggest this lack of response was from imbalances in viral susceptibility to the optimized background regimens.

In children aged 2 to <12 years, tenofovir 8 mg/kg/dose once daily showed non-inferiority to zidovudine- or stavudine-containing cART over 48 weeks of randomized treatment using a snapshot analysis (product label). This was a switch study in children aged 2 to 12 years with viral load <400 copies/mL during treatment with zidovudine or stavudine as part of cART, randomized to continue their zidovudine or stavudine (N = 49) or switch to tenofovir (N = 48) while continuing other components of the regimen (Gilead study 352).[4]

Other pediatric studies have also shown that virologic success is related to prior treatment experience. In 115 pediatric patients treated with tenofovir, viral load decreased to <50 copies/mL at 12 months in 50% of patients on first-line therapy, 39% of patients on second-line therapy, and 13% of patients on third-line or subsequent therapy.[7] This cohort used a target dose of 8 mg/kg, but 18% of patients were dosed at greater than 120% of the target dose and 37% were dosed at less than 80% of the target dose.

Pharmacokinetics

Relationship of Drug Exposure to Virologic Response and Toxicity

Virologic success is related to drug exposure. In a study using a median daily dose of 208 mg/m^2,[8] lower single-dose and steady-state area under the curve (AUC) were associated with inferior virologic outcome.

Pharmacokinetic (PK) studies in children receiving an investigational 75-mg tablet formulation of tenofovir showed that a median dose of 208 mg/m^2 of body surface area (range 161–256 mg/m^2 body surface area) resulted in a median single dose AUC and maximum plasma concentration (C_{max}) that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg.[1,9] Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure.[1] This lower exposure occurred even though participants were concurrently treated with ritonavir, which boosts tenofovir exposure. Lower-than-anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir.[10]

Further studies are needed of tenofovir PK and clinical outcomes in children, especially when used in combinations that do not include lopinavir and/or ritonavir.

Formulations

Special Considerations

The taste-masked granules that make up the oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed in the vehicle, tenofovir should be administered promptly because, if allowed to sit too long, its taste becomes bitter.

Toxicity

Bone

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (i.e.,Tanner Stages 1 and 2) may be at higher risk than children with more advanced development (i.e., Tanner Stage ≥3).[1,11,12] In a Phase I/II study of an investigational 75-mg formulation of tenofovir in 18 heavily pretreated children and adolescents, a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DXA) scan was reported in 5 of 15 (33%) children evaluated at Week 48.[1] Two of the 5 children who discontinued tenofovir at 48 weeks experienced partial or complete recovery of BMD by 96 weeks.[13] Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years.[8,13] In a second study of 6 patients who received the commercially available, 300 mg formulation of tenofovir, 2 pre-pubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her cART regimen with subsequent recovery of BMD.[14] Loss of BMD at 48 weeks was associated with higher drug exposure.[8]

In the industry-sponsored study that led to FDA approval of tenofovir in adolescents aged ≥12 years and weight ≥35 kg, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm[4,5] (see http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM209151.pdf).

In the Gilead switch study (352) in children aged 2 to 12 years over the 48 weeks of randomized treatment, total body BMD gain was less in the tenofovir group than in the zidovudine or stavudine group, but the mean rate of lumbar spine BMD gain was similar between groups. At 48 weeks all participants were offered tenofovir, and for the participants who were treated with the drug for 96 weeks, total body BMD *z* score declined by -0.338 and lumbar spine BMD *z* score declined by -0.012.[4]

Not all studies of tenofovir in children have identified a decline in BMD.[15,16] No effect of tenofovir on BMD was found in a study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz.[17] All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen.[18]

Monitoring

The Panel does not recommend routine DXA monitoring for children or adolescents treated with tenofovir. Given the potential for BMD loss in children treated with tenofovir, some experts recommend obtaining a DXA before initiation of tenofovir therapy and approximately 6 months after starting tenofovir, especially in pre-pubertal patients and those early in puberty (i.e., Tanner Stages 1 and 2). Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in early adolescence is concerning and favors judicious use of tenofovir in this age group.

Renal

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in those with higher tenofovir trough plasma concentrations.[19] Possible tenofovir-associated nephrotoxicity manifests as Fanconi syndrome, reduced creatinine clearance (CrCl), and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including ritonavir-boosted lopinavir and didanosine for 1 year.[20] Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine.[21] Renal toxicity leading to discontinuation of tenofovir was reported in 3.7% (6 of 159) of HIV-1-infected children treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland.[7] Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 27% (12 of 44) of children treated with tenofovir compared with 4% (2 of 48) of children not treated with tenofovir.[22] An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing cART.[23] Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovir-containing antiretroviral regimens from 5 Spanish hospitals. The patients ranged in age from 8 to 17 years (median age 12.5 years) and had received tenofovir for 16 to 143 months (median 77 months). The following observations were made: 18 patients had declines in CrCl after at least 6 months of therapy; 28 patients had decreases in tubular reabsorption of phosphate, which worsened with longer time on tenofovir; and 33 patients had proteinuria, including 10 patients with proteinuria in the nephrotic range.[24] However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years.[25] Of 89 participants who received tenofovir in Gilead study 352 (median drug exposure 104 weeks), 4 discontinued from the study for renal tubular dysfunction, 3 of whom had hypophosphatemia and decrease in total body or spine BMD *z* score.[4]

Monitoring

Because of the potential for tenofovir to decrease creatinine clearance and to cause renal tubular dysfunction, it is recommended to measure serum creatinine and urine dipstick for protein and glucose prior to drug initiation. In an asymptomatic person, the optimal frequency for routine monitoring of creatinine and renal tubular function (urinalysis or urine protein) is unclear. Many panel members monitor creatinine with other laboratory 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.

Tenofovir has antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection, please see the [Pediatric Opportunistic Infections guidelines](http://aidsinfo.nih.gov/guidelines/html/5/pediatric-oi-prevention-and-treatment-guidelines/0).

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Zidovudine (ZDV, AZT, Retrovir) (Last updated February 12, 2014; last reviewed February 12, 2014)

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: Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

Combination Tablets:

With lamivudine:

- 300 mg zidovudine plus 150 mg lamivudine (Combivir, generic)

With lamivudine plus abacavir:

- 300 mg zidovudine plus 150 mg lamivudine plus 300 mg abacavir (Trizivir)

Dosing Recommendations

Zidovudine Dose For Neonates/Infants (Aged <6 Weeks) For Prevention Of Transmission Or Treatment

Note: Standard neonate dose may be excessive in premature infants

Gestational Age (Weeks)	Zidovudine Oral Dosing	Zidovudine Intravenous Dosing (If Unable to Tolerate Oral Agents)
≥35 weeks	4 mg/kg body weight every 12 hours	3 mg/kg body weight IV every 12 hours
≥30 to <35 weeks	2 mg/kg body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days	1.5 mg/kg body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days
<30 weeks	2 mg/kg body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks	1.5 mg/kg body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks

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 and platelets.

Pediatric Dose (Aged 6 Weeks to <18 Years)

Body Surface Area Dosing:

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

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

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

- Metabolized to zidovudine glucuronide, which is renally excreted.
- 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 Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

* Three-times-daily dosing is approved but rarely used in clinical practice.

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]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) 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.[3]

Pediatric Use

Approval

Zidovudine is frequently included as a component of the NRTI backbone for combination antiretroviral therapy (cART).[4-20] Pediatric experience with zidovudine both for treatment of HIV and for prevention of perinatal transmission is extensive.

Efficacy and Dosing (PMTCT or Treatment)

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%[21] (see the Perinatal Guidelines for further discussion on the use of zidovudine for PMTCT 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 is now recommended for neonates/infants >35 weeks of gestation for prevention of transmission or treatment (see the Perinatal Guidelines).

Pharmacokinetics

Overall, zidovudine pharmacokinetics (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.[22] 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.[5] 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.[23]

Toxicity

While the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since the routine use of cART, a regimen containing zidovudine may increase the risk.[24] Recent analysis of data from a U.S.-based, multicenter prospective cohort study (PACTG 219/219C) found that ongoing zidovudine exposure was independently associated with a higher rate of cardiomyopathy.[24]

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Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence, TMC 125)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant, TMC 278)

Efavirenz (EFV, Sustiva) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Combination Tablets:

With Emtricitabine and Tenofovir Disoproxil Fumarate (Tenofovir):

- Emtricitabine 200 mg + Tenofovir 300 mg + Efavirenz 600 mg (Atripla)

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 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 and at age 3 years for possible 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 (CNS) symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures
- 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 CNS 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.

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

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor)
- CYP2B6, CYP3A4, and CYP2A6 substrate
- 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 tenofovir and emtricitabine require dose adjustment based on renal function, Atripla should not be used in patients with creatinine clearance (CrCl) <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.)

- *Metabolism:* Mixed inducer/inhibitor of CYP3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. 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, lopinavir/ritonavir, 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 concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.
- *Rare:* Potential risk of teratogenicity. Classified as Food and Drug Administration (FDA) Pregnancy Class D, which means that there is positive evidence of human fetal risk based on studies in humans (see Pediatric Use section below; see also the Perinatal Guidelines.[1]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/EFV.html).

Pediatric Use

Approval

Efavirenz is FDA-approved for use as part of combination antiretroviral therapy in children aged 3 months or older who weigh at least 3.5 kg.

Pharmacokinetics (PK): 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.[2-4] 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.[4] Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years.[4] Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.[5-8]

PK and Dosing: Infants and Children Aged <3 Years

Limited 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.[4,9] Hepatic enzyme activity is known to change with age. 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.[2] In children with CYP 2B6-516-G/G genotype, oral clearance rate has been shown to be higher in children younger than aged 5 years than in older children.[2] Efficacy data in infants and young children are mostly limited to studies of liquid efavirenz formulations, such as in PACTG 382 and PACTG 1021, and showed poor virologic response due to variable PK properties and tolerability of the liquid formulations in this young age group. Liquid formulations are not approved for use or available in the United States. Efficacy data for opened capsules with contents used as sprinkles suggest better 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.[4] When used without regard to genotype, doses higher than the FDA-recommended ones 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.[4] 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.

Tables 1a and 1b

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

Table 1a. For Patients with CYP 2B6 516 GG and GT Genotypes (Extensive Metabolizers)*

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. For patients with CYP 2B6 516 TT genotype (slow metabolizers)*

Weight (kg)	Efavirenz Dose (mg)
3 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

* Investigational doses are based on IMPAACT study P1070.[4] 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 adult subjects in PACTG 1021 and PACTG 382, and AI266-922, which is an ongoing 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. 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 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, efavirenz concentrations should be measured at age 3 years to guide potential dose adjustments.

PK: 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.[10] 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).[11] 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 area under the curve (AUC) > 51 mcg h/mL.[12]

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, efavirenz concentrations can be suboptimal.[2,12-16] Therefore, some experts recommend therapeutic drug monitoring 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).[11] A PK study in 20 children aged 10 to 16 years treated with the combination of 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.[17] Therapeutic drug monitoring can be considered when using efavirenz in combinations with potentially complex drug interactions.

Dosing: Special Considerations

For patients at least 3 months old who cannot swallow capsules or tablets, the efavirenz capsule contents can be administered with a small amount (1 to 2 teaspoons) of food. Use of 2 teaspoons of infant formula can be considered for infants who cannot reliably consume solid foods. The capsule should be held horizontally over a small container and carefully twisted open to avoid spillage and dispersion of capsule contents into the air. The capsule contents should be gently mixed with an age-appropriate soft food, such as applesauce, grape jelly, or yogurt, or reconstituted infant formula at room temperature, in a small container. The infant formula mixture should be administered 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. The efavirenz mixture should be administered within 30 minutes of mixing and no additional food or formula should be consumed for 2 hours after administration.

Toxicity: Children versus Adults

The toxicity profile for efavirenz differs for adults and children. A side effect commonly seen in children is rash, which was reported in up to 40% of children compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment.[18] 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.[19] 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 adverse effects. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations.[10,20-23] In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies[18] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.[3] 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. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in five infants after first-trimester exposure to efavirenz-containing regimens (three reports of meningomyeloceles and two of Dandy-Walker malformations), efavirenz has been classified as FDA Pregnancy Class D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible.[24] 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 the Perinatal Guidelines.[1]

Therapeutic Drug Monitoring

Note: see Role of Therapeutic Drug Monitoring.

In the setting of potential toxicity, it is reasonable for a clinician to use therapeutic drug monitoring (TDM) to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.[25,26] 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. 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.[10] In addition, efavirenz concentrations should be measured 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 February 12, 2014; last reviewed February 12, 2014)

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 currently underway.

Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years (and Weighing at Least 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.

Special Instructions

- Always administer etravirine following a meal. Area under the curve (AUC) 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 at least enough liquid to cover the medication and stir well until the water looks milky. If desired, add more water or alternatively orange juice or milk (**Note:** Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm [>40°C] drinks, or carbonated beverages should be avoided.) Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Dosing of etravirine in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

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

Metabolism

- 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 drug interactions (see text below).

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

- 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, atazanavir/ritonavir, and unboosted protease inhibitors. It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., 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.

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, 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ETR.html).

Pediatric Use

Approval

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

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 subjects aged 6 to <18 years and weighing ≥16 kg.[2] Subjects eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA of at least 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 protease inhibitor plus nucleoside analogue reverse transcriptase inhibitors and optional enfuvirtide and/or raltegravir. At week 24, 67% of these pediatric subjects had plasma HIV-1 RNA concentrations <400 copies/mL and 52% had <50 copies/mL. At week 48, 56% of the subjects had <50 copies/mL, with a mean CD4 T lymphocyte cell increase of 156 x106/mm^3.[3] A greater fraction of children aged 6 to <12 years had plasma HIV RNA-1 <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 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).[4] 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 multi-center retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit, et al. found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥4,[5] 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 twice daily. The PK parameters AUC_{12h} and C_{min} were below preset statistical targets based on prior studies involving adults.[6] 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 adults and younger children.

Participants	Mean AUC_{12} (ng*h/mL)	Mean C_{0h} (ng/mL)
Children Aged 6–11 Years (N = 41)	5764	381
Adolescents Aged 12–17 Years (N = 60)	4834	323
All Pediatric Participants	5236	347
Adults	5506	393

AUC_{12} = Area under the curve for 12 h post-dose; C_{0h} = pre-dose concentration during chronic administration.

Etravirine is often combined with ritonavir-boosted darunavir 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] these data suggest a need for continued study of PK interactions involving etravirine and other ARV agents in pediatric patients.

Toxicity

The frequency, type, and severity of adverse drug reactions in pediatric subjects enrolled in the PIANO trial were comparable to those reported in adult subjects, except for rash, which was observed more frequently in pediatric subjects. The most common adverse drug reactions (in at least 2% of pediatric subjects) were rash and diarrhea. Rash (≥Grade 2) occurred in 15% of pediatric subjects. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The discontinuation rate for rash was 4%. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared with male subjects.

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Nevirapine (NVP, Viramune) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Dosing Recommendations

Neonate/Infant Dose (≤14 Days):

- When used for prevention of perinatal transmission of HIV see Perinatal Guidelines.
- Treatment dose is undetermined for infants aged ≤14 days (see Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants)

Pediatric Dose Immediate Release Formulation (>15 Days):

- See note below about initiation of therapy.

<8 Years:

- 200 mg/m^2 of body surface area (BSA)/dose (maximum dose of immediate release tablets is 200 mg twice daily).

≥8 Years:

- 120–150 mg/m^2 BSA/dose (maximum dose of immediate release tablets is 200 mg twice daily or extended release tablets 400 mg once 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.

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 once daily 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 dose administered twice daily. However, in children ≤2 years of age some experts initiate nevirapine without a lead-in

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

- 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 XR tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for >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 (LFTs), is important during this period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of LFTs is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have LFTs performed. Nevirapine should be permanently

(see Dosing Considerations: Lead-In Requirement). The total daily dose should not exceed 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 XR without lead-in dosing as long as plasma RNA is undetectable.

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)

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 once daily 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 dose administered **once daily for the XR preparation**. The total daily dose should not exceed 400 mg.

Adolescent/Adult Dose:

- 200 mg twice daily or 400 mg XR once daily.

Note: For 200-mg regimen, initiate therapy with 200 mg once daily for the first 14 days and increase to 200 mg twice daily if there is no rash or other untoward effects. For 400-mg XR regimen, initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release nevirapine, XR tablets can be used without the 200-mg lead-in period. Patients must swallow nevirapine XR tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of nevirapine at the same time.

Nevirapine In Combination with Ritonavir-Boosted Lopinavir:

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

discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.

- Shake suspension well and store at room temperature.

Metabolism

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (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.

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

- 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] 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).

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 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, recent results indicate that 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NVP.html).

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. It has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI).[3-11] In November 2012 the extended release tablet formulation was 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, combination antiretroviral therapy (cART) is less likely than ritonavir-boosted lopinavir-based cART 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 ritonavir-boosted lopinavir. 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/ritonavir-boosted lopinavir, $P = 0.0009$. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the ritonavir-boosted lopinavir arm, $P = 0.027$.[12] Enrollment into the comparison study of nevirapine versus LPV/r in children aged 6 to 36 months **not** previously exposed to nevirapine has reported similar results, suggesting that ritonavir-boosted lopinavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[13]

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients based on two trials: VERxVE and TRANxITION. VERxVE[14] enrolled treatment-naive adults who received 200 mg of immediate-release nevirapine for 14 days before commencing daily dosing of nevirapine extended release or standard twice-daily dosing of immediate-release tablets. A backbone of tenofovir and emtricitabine was used. TRANxITION enrolled patients already receiving full-dose immediate-release nevirapine and randomized them to receive the extended-release tablets or remain on their current nevirapine regimen. Both studies have shown equivalent efficacy, adverse effect, and CD4 profiles through 144 weeks.[15-17] Trial 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial performed in 85 HIV-1 infected pediatric subjects 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. Subjects were stratified according to age (3 to <6 years, 6 to <12 years, and 12 <18 years). Following a 10-day period with immediate-release nevirapine, subjects were treated with nevirapine XR tablets once daily in combination with other antiretrovirals (ARVs) for 10 days, after which steady-state pharmacokinetics were determined. Forty subjects 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 XR through a minimum of 24 weeks of treatment. Of the 40 subjects who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with nevirapine XR, all 39 subjects continued to have plasma HIV-1 RNA less than 50 copies per mL. This dosage form was approved for use in children aged ≥6 years in November 2012.

General Dosing Considerations

Body surface area (BSA) has traditionally been used to guide nevirapine dosing for infants and young children. It is important to avoid under-dosing of nevirapine because a single point mutation 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 younger than age 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 body surface area 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 and older, 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 the re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditional dosing of nevirapine is initiated with an age appropriate dose once daily (200 mg/m^2 in infants ≥15 days of age and children <8 years using the immediate release preparations) during the first 2 weeks of treatment to allow for the auto-induction 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.[18] The CHAPAS-1 Trial[19] randomized 211 children to initiate cART 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 two 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 sub-study of this trial, the investigators looked at nevirapine levels 3 to 4 hours after a morning dose of nevirapine after 2 weeks of therapy. For children <2 years of age, 13% (3/23) initiating at full dose versus 32% (7/22) initiating at half dose had subtherapeutic NVP levels (<3 mg/L) at 2 weeks (p = 0.16). There were no rash events in the substudy group aged <2 years and in the parent CHAPAS study there was a strong age effect on rash occurrence (increased risk with increasing age), suggesting that a lead-in dose may not be necessary in young patients.[20] Additional trials are in development or are underway to further evaluate the potential of initiating nevirapine therapy without the lead-in dose in treatment-naive children. Reinitiating half-dose nevirapine for another 2 weeks in those 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,[21] 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 ≤14 Days and Premature Infants

For infants aged ≤14 days and for premature infants (until 42 weeks corrected gestational age), pharmacokinetic (PK) data are currently inadequate to formulate an effective complete cART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of cART. Reports of cardiovascular, renal, and central nervous system toxicity associated with ritonavir-boosted lopinavir in young infants preclude the administration of this agent in the first 2 weeks of life. Currently, a study of early treatment is being developed in the International Maternal Pediatric Adolescent AIDS Clinical Trials network; based on PK modeling, an investigational dose of 6 mg/kg administered twice daily for nevirapine in full-term infants will be tested. Providers considering treatment of infants aged <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will involve weighing the risks and benefits of using unapproved cART dosing, and incorporate case-specific factors such as exposure to ARV prophylaxis.

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Rilpivirine (RPV, Edurant, TMC 278) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

Tablet: 25 mg

Combination Tablet:

With Emtricitabine and Tenofovir Disoproxil Fumarate (Tenofovir):

- Rilpivirine 25 mg + Emtricitabine 200 mg + Tenofovir 300 mg (Complera)

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children. A clinical trial in treatment-naive adolescents (aged 12–18 years) is under way using a 25-mg dose.

Adolescent (>18 years)/Adult Dose (Antiretroviral-Naive Patients Only):

- 25 mg once daily

Selected Adverse Events

- Depression, mood changes
- Insomnia
- Headache
- Rash

Special Instructions

- Instruct patients to take rilpivirine with a meal of at least 500 calories (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 (http://www.qtdrugs.org/).
- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

Metabolism

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- 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

- *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.

Major Toxicities

- *More common:* Insomnia, headache, and rash
- *Less common (more severe):* Depression or mood changes

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html).

Pediatric Use

Rilpivirine is approved in combination with other ARV agents for treatment-naive, HIV-infected adults with viral load ≤100,000 copies/mL. The pharmacokinetics, safety, and efficacy of rilpivirine in pediatric patients have not been established. An international trial currently under way is investigating a 25-mg dose of rilpivirine in combination with two nucleoside reverse transcriptase inhibitors in antiretroviral-naive children aged 12 to <18 years who weigh ≥32 kg and have a viral load ≤100,000 copies/mL.[1]

Reference

1. ClinicalTrials.gov. A Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Antiviral Efficacy of TMC278 in Human Immunodeficiency Virus Infected Adolescents. ClinicalTrials.gov Identifier: NCT00799864. Available at http://clinicaltrials.gov/show/NCT00799864.

Protease Inhibitors (PIs)

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Fosamprenavir (FPV, Lexiva)

Indinavir (IDV, Crixivan)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Nelfinavir (NFV, Viracept)

Ritonavir (RTV, Norvir)

Saquinavir (SQV, Invirase)

Tipranavir (TPV, Aptivus)

Atazanavir (ATV, Reyataz) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

Capsules: 150 mg, 200 mg, and 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants. ATV should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric Dose:

- Data are insufficient to recommend dosing in children aged <6 years.

For Children Aged ≥6 to <18 Years

Weight (kg)	Once-Daily Dose
15 to <20 kg	ATV 150 mg plus RTV 100 mg, both once daily with food
20 to <40 kg	ATV 200 mg plus RTV 100 mg, both once daily with food*
≥40 kg	ATV 300 mg plus RTV 100 mg, both once daily with food

* Some experts would increase ATV to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with tenofovir (see text for discussion)

For Treatment-Naive Pediatric Patients who do not Tolerate Ritonavir (RTV):

- **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.** Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children aged <13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see Pediatric Use).
- Only RTV-boosted ATV should be used in combination with tenofovir disoproxil fumarate (TDF) because TDF decreases ATV exposure.

Adolescent (Aged ≥18 to 21 Years)/Adult Dose

Antiretroviral-Naive Patients:

- ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food (if unboosted ATV is

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram (ECG) PR interval, first-degree symptomatic atrioventricular (AV) block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with RTV boosting)

Special Instructions

- Administer ATV with food to enhance absorption.
- Because ATV can prolong the ECG PR interval, use ATV with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions for recommendations on dosing ATV when the drug is co-administered with H2 receptor antagonists). When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is co-administered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients receiving PPIs should receive no more than a 20-mg dose equivalent of

used in adolescents, higher doses than those used in adults may be required to achieve target drug levels [see Pediatric Use]).

Antiretroviral-Experienced Patients:

- ATV 300 mg + RTV 100 mg, both once daily with food.

ATV In Combination With Efavirenz (EFV) (Adults) In Therapy-Naive Patients Only:

- ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily at separate times.
- Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be co-administered with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure.

ATV In Combination With TDF (Adults):

- ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food.
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

omeprazole, which should be taken approximately 12 hours before boosted ATV. Co-administration of ATV 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.

Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucoronosyltransferase (UGT1A1).
- Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

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

- *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. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.
- A patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug is administered.
- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir disoproxil fumarate (tenofovir) decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.
- *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.

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 antiretroviral (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 -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 tenofovir):* Treatment-experienced patients using both tenofovir and H2-receptor antagonists should be given an increased dose of atazanavir (atazanavir 400 mg plus ritonavir 100 mg plus tenofovir 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 + ritonavir 100 mg). Co-administration of atazanavir with PPIs is not recommended in treatment experienced patients.

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. 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 protease inhibitors (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 pre-existing 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ATV.html).

Pediatric Use

Approval

Atazanavir is FDA-approved for use in children and adolescents. Ritonavir-boosted atazanavir is generally preferred over unboosted atazanavir and is used in combination with NRTIs for treatment in children aged ≥6 years.

Pharmacokinetics and Dosing

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 pharmacokinetic (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 older than 6 but younger than 13 years of age required atazanavir dosing of 520 mg/m^2 per day of atazanavir capsule formulation to achieve PK targets. 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.[1] In this study, the areas under the curve (AUCs) for the unboosted arms were similar to the ritonavir-boosted atazanavir 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.[2] Higher target trough concentrations may be required inPI-experienced patients.

Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A[1]

Age Range (Years)	Was ATV Given with RTV Boosting?	ATV Median Dose (mg/m^2*)	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

* 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.

In the report of the P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m^2 in pediatric subjects when dosed with ritonavir.[1] However, given the available atazanavir capsule dose strengths, it is not possible to administer the exact mg dose equivalent to the body surface area-based dose. A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A) supports the use of the following weight-based atazanavir/ritonavir 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)[3]

The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.[3] The authors acknowledge that atazanavir/ritonavir at 250/100 mg appeared to be a more appropriate dose than atazanavir/ritonavir 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).[3] Some experts would increase ATV to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with tenofovir.

A third pediatric study of atazanavir, a population PK study of 51 children with mean age 14.3 years and weight 51 kg that targeted mean adult exposure for a 300/100 mg atazanavir/ritonavir dosage, showed that the following atazanavir/ritonavir doses might be an appropriate alternative to the FDA recommendations: 200/100 (25–39 kg), 250/100 mg (39–50 kg) and 300/100 (>50 kg).[4] In addition, simulations suggested that the following doses should be used in children when combined with 300 mg tenofovir: 250/100 mg for children weighing 35 to 39 kg, then 300/100 mg for children weighing over 39 kg.[4] The authors conclude that these recommendations should be prospectively confirmed.[4] Again, the 250-mg dose is not achievable with current capsule dose strengths and some experts would increase ATV to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with tenofovir.

Toxicity

8.5% (11 of 129) of patients enrolled in the IMPAACT/PACTG 1020A trial had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram 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.[5,6]

References

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5. Rutstein R, Samson P, Aldrovandi G, Graham B, Schnittman S, Fenton T. Effect of Atazanavir on Serum Cholesterol and Triglycerides in HIV-Infected Infants, Children and Adolescents: Pediatric AIDS Clinical Trials Group 1020A. Poster 774. 12th Conference on Retroviruses and Opportunistic Infections (CROI); February 20, 2005; Boston, MA.
6. Bristol-Myers Squibb. Reyataz (atazanavir sulfate) package insert. Revised April 2013. Available at: www.reyataz.com.

Darunavir (DRV, Prezista) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

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

Oral suspension: 100 mg/mL

Dosing Recommendations

Note: DRV should not be used without low-dose boosting ritonavir (RTV).

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

Aged <3 years:

- **Do not use DRV 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.
- The dosing for antiretroviral **treatment-naive and treatment-experienced** pediatric patients aged ≥3 years (includes patients with or without one or more DRV resistance-associated mutations)

Aged 3 to <18 Years and Weight >10kg

Weight (kg)	Dose (twice daily with food)
10 to <11 kg[a]	DRV 200 mg (2.0 mL) plus RTV 32 mg (0.4 mL)
11 to <12 kg[a]	DRV 220 mg (2.2 mL) plus RTV 32 mg (0.4 mL[b])
12 to <13 kg[a]	DRV 240 mg (2.4 mL) plus RTV 40 mg (0.5 mL[b])
13 to <14 kg[a]	DRV 260 mg (2.6 mL) plus RTV 40 mg (0.5 mL[b])
14 to <15 kg	DRV 280 mg (2.8 mL) plus RTV 48 mg (0.6 mL[b])
15 to <30 kg	DRV 375 mg (combination of tablets or 3.8 mL[c]) plus RTV 48 mg (0.6 mL[b])
30 to <40 kg	DRV 450 mg (combination of tablets or 4.6 mL[c]) plus RTV 100 mg (tablet or 1.25 mL[b])
≥40 kg	DRV 600 mg (tablet or 6 mL) plus RTV 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 DRV-associated mutation(s), DRV should be used only twice daily. **DRV resistance-associated mutations are:** V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- DRV 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.
- DRV contains a sulfonamide moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV 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 DRV tablets and oral suspension at room temperature (25°C or 77°F). Oral suspension should be stored in the original container and shaken well before dosing.

[a] Note that the dose in children weighing 10–15 kg is 20 mg/kg DRV and 3 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 g/mL oral solution.

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

Adolescent (Aged ≥12 Years)/Adult Dose (Treatment-Naive or Antiretroviral Therapy-Experienced with no DRV Resistance-Associated Mutations)

30 to <40 kg:

- DRV 675 mg (combination of tablets or 6.8 mL[a]) plus RTV 100 mg (tablet or 1.25 mL[b]) **once daily**

≥40 kg:

- DRV 800 mg (tablet or combination of tablets or 8 mL) plus RTV 100 mg (tablet or 1.25 mL[b]) **once daily**

[a] The 675 mg DRV dose is rounded for convenience.

[b] RTV 80 mg/mL oral solution.

Adolescent (Aged ≥18 Years)/Adult Dose (Treatment Experienced with at Least One DRV Resistance-Associated Mutation):

- DRV 600 mg plus RTV 100 mg, both **twice daily** with food.

Metabolism

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

Dosing in Patients with Hepatic Impairment:

- DRV 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 DRV to such patients. DRV 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 pharmacokinetic data 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)

- Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. Potential exists for multiple drug interactions. Co-administration of darunavir/ritonavir is contraindicated with drugs that are highly dependent on the CYP3A clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
- When darunavir plus ritonavir twice daily was used 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 plus ritonavir twice daily was used in combination with tenofovir in 13 HIV-infected patients aged 13 to 16 years, both tenofovir and darunavir exposures were lower than those found in adults treated with the same combination.[2] No dose adjustment is currently recommended for the combination of darunavir/ritonavir with either of these drugs, but caution is advised and therapeutic drug monitoring 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.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (such as hepatitis B or hepatitis C virus coinfection, or those with baseline elevation in transaminases).

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/DRV.html).

Pediatric Use

Approval

Darunavir co-administered with ritonavir is approved by the Food and Drug Administration (FDA) as a component of combination antiretroviral therapy 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 clinical trial (TMC114-C228) involving 27 children (3 to <6 years of age) from Argentina, Brazil, India, Kenya, and South Africa, 59% of children (out of 27) and 71% (out of 20) had viral load <50 copies/mL at week 24 and at week 48, respectively.[3-6]

Pharmacokinetics

Pharmacokinetics in Younger Children

Administration of twice-daily ritonavir-boosted darunavir 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 antiretroviral therapy regimen and had fewer than 3 darunavir resistance mutations on genotypic testing.[3-5] The darunavir $AUC_{(0–12h)}$, 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.[3-5]

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, multi-center study that enrolled 80 treatment-experienced children and adolescents aged 6 to <18 years and weighing ≥20 kg.[7] 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 area under the curve $(AUC)_{24h}$ 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 123276 ng*h/mL (range 71850–201520) 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 ritonavir-boosted darunavir 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] FDA pharmacokinetics review 2011 (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 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf)

[c] Product label

Dosing

Dosing of Ritonavir with Darunavir

A separate 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).[8] 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.[7,8] 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.

Frequency of Administration

In February 2013, FDA approved the use of darunavir once daily 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.[6] 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 only twice daily in children aged >3 years and <12 years. The Panel recommends that once-daily darunavir with ritonavir be used only in treatment-naive and treatment-experienced adolescents aged ≥12 years and without 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 and inhibitory quotient) evaluation (see Therapeutic Drug Monitoring) and close monitoring of viral load.

FDA approval was based on the 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).[6,9,10]

Table B. FDA-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weight >10 Kg Who Are Antiretroviral Treatment-Naive or Treatment-Experienced With No DRV 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 10–15 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 (3.4 mL and 4 mL, respectively) administrations with the included oral dosing syringe, or as one syringe when provided by pharmacy or medical office.

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.[6,11] The ritonavir-boosted darunavir 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 ritonavir-boosted darunavir 600 mg/100 mg once daily for children weighing ≥15 kg.[6,11] The PK data obtained from 10 children aged 3 to 6 years in this sub-study (Table C) were included as part of the population PK modeling and simulation, which proposed the FDA-approved dose for once-daily darunavir with ritonavir in children aged 3 to <12 years.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3–6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone.[11]

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*)	3029 (1715)	2027 (1168)

*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).[9] In this study, the proportion of patients with viral load <50 copies/mL and <400 copies/mL at 48 weeks was 83.3% and 91.7%, respectively.[9,10] Interestingly, no relationship was observed between darunavir AUC_{24h} and C_{0h} and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those in adults with once-daily dosing in another study in which a single dose darunavir 800 mg with ritonavir 100 mg tablets was administered to 24 subjects with median age 19.5 years (14–23 years).[12] However, darunavir exposures were slightly below the lower target concentrations in adolescent patients age 14 to 17 years (n = 7) within the cohort, suggesting the potential need for higher doses in younger adolescents. A single case report suggests the potential therapeutic benefit of virologic suppression using an increased darunavir dose with standard ritonavir booster following therapeutic drug monitoring in a highly treatment-experienced adolescent patient.[13]

Table D. Darunavir Pharmacokinetics with Once-Daily Administration (Adolescents Aged ≥12 Years and Adults Aged >18 Years)

Population	N	Dose of DRV/RTV	AUC_{24h}[a] (mcg*h/mL) median	C_{0h} (ng/mL) median
Aged 12–17 years (mean 14.6)[9]	12	800/100 mg	86.7	2,141
Aged 14–23 years (mean 19.5)[12]	24	800/100 mg	69.5	1,300
Adults aged >18 years (2 studies)[a]	335/280	800/100 mg	87.8–87.9	1,896–2,041

[a] Product label

The efficacy of once-daily darunavir has been established only within a small cohort of adolescent patients with 48 weeks data on virologic and immunologic outcomes.[9,10]

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.[7] Switching to the higher dose of ritonavir for the palatability of the boosting drug can be considered if the liquid formulation represents a barrier.

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Fosamprenavir (FPV, Lexiva) (Last updated February 12, 2014; last reviewed February 12, 2014)

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 at least 4 weeks of age and for treatment-experienced infants at least 6 months of age; 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.

Aged ≥6 Months to 18 Years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients at Least 6 Months of Age Using Lexiva Oral Suspension with Ritonavir

Weight	Dose Fosamprenavir Plus Ritonavir Both twice daily* with food
<11 kg	fosamprenavir 45 mg/kg plus ritonavir 7 mg/kg
11 kg to <15 kg	fosamprenavir 30 mg/kg plus ritonavir 3 mg/kg
15 kg to <20 kg	fosamprenavir 23 mg/kg plus ritonavir 3 mg/kg
≥20 kg	fosamprenavir 18 mg/kg plus ritonavir 3 mg/kg

* 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. Pediatric patients 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

- The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.
- Amprenavir is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.

Note: When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing ≥39 kg. Ritonavir pills can be used in patients weighing ≥33 kg.

Once-daily dosing is not recommended for any pediatric patient.

Adolescent/Adult (Aged >18 Years) Dose:

- Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

RV-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)

- Fosamprenavir has the potential for multiple drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.

Major Toxicities

- *More common:* Vomiting, nausea, diarrhea, perioral paresthesia, headache, rash, and lipid abnormalities.
- *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing 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%–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 AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/APV_fosamprenavir.html).

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 3 pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In 2 open-label trials in both treatment-experienced and treatment-naive children from ages 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 age 4 weeks and in treatment-experienced infants as young as age 6 months.[1] Exposures in those younger than age 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 volumes, unpleasant taste, and the availability of alternatives for infants and young children, the Panel does not recommend fosamprenavir use in infants younger than 6 months.

Population	Dose	$AUC_{0\text{-}24}$ (mcg*hr/mL) Except Where Noted	C_{min} (mcg/mL)
Infants <6 months	45 mg fosamprenavir/10 mg ritonavir per kg twice daily	26.6[a]	0.86
Children aged 2 to <6 years	30 mg fosamprenavir per kg twice daily (no ritonavir)	22.3[a]	0.513
Children weighing <11 kg	45 mg fosamprenavir/7 mg ritonavir per kg twice daily	57.3	1.65
Children weighing 15 to <20 kg	23 mg fosamprenavir/3 mg ritonavir per kg twice daily	121.0	3.56
Children weighing ≥20 kg	18 mg fosamprenavir/3 mg ritonavir per kg twice daily (maximum 700/100 mg)	72.3–97.9	1.98–2.54
Adults	1400 mg fosamprenavir twice daily (no ritonavir)	33	0.35
Adults	1400 mg fosamprenavir/100–200 mg ritonavir once daily	66.4–69.4	0.86–1.45
Adults	700 mg fosamprenavir/100 mg ritonavir twice daily	79.2	2.12

[a] $AUC_{0\text{-}12}$ (mcg*hr/mL)

Note: Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies, therefore, area under the curve and C_{min} are not available.

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Indinavir (IDV, Crixivan) (Last updated November 1, 2012; last reviewed February 12, 2014)

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

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate
- Dosing in patients with hepatic impairment: Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

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

- *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 pre-existing 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 AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ indinavir.html).

Pediatric Use

Approval

Indinavir has not been approved by the Food and Drug Administration (FDA) 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 ritonavir-boosted indinavir 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%–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 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 February 12, 2014; last reviewed February 12, 2014)

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 ritonavir-boosted lopinavir per m^2 of body surface area twice daily (approximates 16 mg/4 mg ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir per m^2 of body surface area per dose twice daily (maximum dose 400 mg/100 mg twice daily except as noted below). For patients with body weight <15 kg, this approximates 13 mg/3.25 mg ritonavir-boosted lopinavir per kg body weight twice daily; and for patients with body weight ≥15 to 45 kg this dose approximates 11 mg/2.75 mg ritonavir-boosted lopinavir per kg body weight twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients with possible 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

- Ritonavir-boosted lopinavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- Ritonavir-boosted lopinavir tablets must be swallowed whole. Do not crush or split tablets.
- Ritonavir-boosted lopinavir oral solution should be administered with food because a high-fat meal increases absorption.
- The poor palatability of ritonavir-boosted lopinavir oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- Ritonavir-boosted lopinavir 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)

- 230 mg/57.5 mg ritonavir-boosted lopinavir/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 ritonavir-boosted lopinavir per kg body weight given twice daily and for patients ≥15 kg to 40 kg, this dose approximates 10 mg/2.5 mg ritonavir-boosted lopinavir per kg body weight given twice daily.

Weight-Band Dosing for 100 mg/25 mg Ritonavir-Boosted Lopinavir Pediatric Tablets for Children/ Adolescents

	Recommended number of 100-mg/25-mg ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir tablets can be substituted by 2 tablets each containing 200 mg/50 mg ritonavir-boosted lopinavir in children capable of swallowing a larger size 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 ritonavir-boosted lopinavir twice daily, given as a combination of 2 tablets of 200/50 mg ritonavir-boosted lopinavir and 1 tablet of 100 mg/25 mg ritonavir-boosted lopinavir. Alternatively, 3 tablets of 200/50 mg ritonavir-boosted lopinavir can be used for ease of dosing.

Adult Dose (>18 Years):

- 800 mg/200 mg ritonavir-boosted lopinavir once daily, **or**
- 400 mg/100 mg ritonavir-boosted lopinavir twice daily.
- Do **not** use once-daily dosing in children or adolescents, or in patients receiving concomitant therapy with nevirapine,

ritonavir-boosted lopinavir oral solution remains stable until the expiration date printed on the label.

- Once-daily dosing is not recommended because of considerable variability in plasma concentrations in children aged <18 years and higher incidence of diarrhea.
- Use of ritonavir-boosted lopinavir 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

- Cytochrome P (CYP) 3A4 inhibitor and substrate.
- Dosing of ritonavir-boosted lopinavir in patients with hepatic impairment: ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir, 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.

efavirenz, fosamprenavir, or nelfinavir, or in patients with three or more lopinavir-associated mutations (see Special Instructions for list).

In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):

- 400 mg/100 mg ritonavir-boosted lopinavir twice daily.

Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir.

Note: These drugs induce lopinavir metabolism and reduce lopinavir plasma levels; increased ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir per m^2 of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult Dose (>18 Years):

- Food and Drug Administration (FDA)-approved dose is 500 mg/125 mg ritonavir-boosted lopinavir twice daily, given as a combination of 2 tablets of 200/50 mg ritonavir-boosted lopinavir and 1 tablet of 100 mg/25 mg ritonavir-boosted lopinavir. Alternatively, 3 tablets of 200/50 mg ritonavir-boosted lopinavir can be used for ease of dosing. Once-daily dosing should **not** be used.

Ritonavir-boosted Lopinavir in Combination with Saquinavir Hard-Gel Capsules (Invirase) or in Combination with Maraviroc:

- Saquinavir and maraviroc 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.)

- *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
- *Less common (more severe):* Fat maldistribution
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases). PR interval prolongation. QT interval prolongation and torsades de pointes may occur.
- *Special populations—neonates:* Ritonavir-boosted lopinavir 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,[1] life-threatening bradyarrhthymias and cardiac dysfunction,[2-4] and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression.[4] 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%.[4] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with ritonavir-boosted lopinavir.[1]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/LPV.html).

Pediatric Use

Approval

Ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir, the appropriate pediatric dose would be approximately 230/57.5 mg ritonavir-boosted lopinavir 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[5-7] are compared to those in older children[8] and adults[9] as shown in the table below.

	Adults[9]	Children[8]	Children[8]	Infants at 12 Months[7,a]	Infants 6 weeks–6 months[5]	Infants <6 weeks[6]
N	19	12	15	20	18	9
Dose Lopinavir	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 according to an e-mail from Edmund Capparelli, PharmD (April 18, 2012)

Note: Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Key to Acronyms: AUC = area under the curve; LPV = lopinavir

Models suggest that diet, body weight and postnatal age are important factors in lopinavir PK, with improved bioavailability as dietary fat increases over the first year of life[10] and with clearance slowing by age 2.3 years.[11] A study from the UK and Ireland in children aged 5.6 to 12.8 years at the time of ritonavir-boosted lopinavir 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 long-term viral load suppression.[12]

Pharmacokinetics and Dosing

Aged 6 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 ritonavir-boosted lopinavir per m^2 of body surface area when compared to the 300 mg/75 mg ritonavir-boosted lopinavir per m^2 of body surface area per dose twice-daily dose. (see table and Verweel, Burger, 2007) Therefore, some clinicians choose to initiate therapy in children aged 6 months to 12 years using 300 mg/75 mg ritonavir-boosted lopinavir per m^2 of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the drug label-recommended 230 mg/57.5 mg ritonavir-boosted lopinavir per m^2 of body surface area per dose twice daily.

For infants receiving 300 mg/75 mg ritonavir-boosted lopinavir 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 ritonavir-boosted lopinavir 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 LPV/r liquid formulation.

Aged 6 Weeks to 6 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

The PK of the oral solution at approximately 300 mg/75 mg ritonavir-boosted lopinavir per m^2 body surface area per dose twice daily was evaluated in infants younger than age 6 weeks[6] and infants aged 6 weeks to 6 months.[5]

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 ages 6 weeks to 6 months. By age 12 months, lopinavir AUC was similar to that found in older children.[7] 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,[13] 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 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 ritonavir-boosted lopinavir per m^2 body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL.[8] Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of ritonavir-boosted lopinavir, but the variability in concentration is much higher in children than adults.[8,14] In a study of 15 HIV-infected children 5.7 to 16.3 years treated with the combination of 300 mg/75 mg ritonavir-boosted lopinavir 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.[15] A PK study in 20 children aged 10 to 16 years treated with the combination of ritonavir-boosted lopinavir 300 mg/75 mg per m^2 body surface area twice daily plus efavirenz 350 mg/m^2 body surface area once daily showed only 1 (6.6%) patient with sub-therapeutic lopinavir trough concentrations,[16] perhaps because of the use of a lower efavirenz dose of approximately 11 mg/kg body weight,[16] compared to efavirenz 14 mg/kg body weight in the Bershoeff trial.[15]

Dosing

Once Daily

Once-daily dosing of ritonavir-boosted lopinavir 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 ARV-naive children and adolescents.[17-20] Compared with the soft-gel formulation of ritonavir-boosted lopinavir, the tablet formulation has lower variability in trough levels[20,21] but the Panel remains concerned about the long-term effectiveness of once-daily ritonavir-boosted lopinavir in children.

Dosing and Its Relation to Efficacy

Ritonavir-boosted lopinavir is effective in treatment-experienced patients with severe immune suppression,[22,23] although patients with greater prior exposure to ARVs may have slower reductions in virus load to undetectable concentrations[23,24] and less robust response in CD4 percentage.[25] 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%.[25]

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 ritonavir-boosted lopinavir, virus load reduction is more closely associated with IQ than with either the C_{trough} or EC_{50} alone.[26-28] A study of the practical application of the IQ to guide therapy using higher doses of ritonavir-boosted lopinavir in children and adolescents to reach a target IQ of 15 showed the safety and tolerability of doses of 400 mg/100 mg ritonavir-boosted lopinavir per m^2 body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine or efavirenz) and 480 mg/120 mg ritonavir-boosted lopinavir per m^2 body surface area per dose twice daily (with nevirapine or efavirenz).[13] Results of a modeling study suggest that standard doses of ritonavir-boosted lopinavir may be inadequate for treatment-experienced children and suggest the potential utility of TDM when ritonavir-boosted lopinavir is used in children previously treated with protease inhibitors.[29]

Formulations

Palatability

The poor palatability of the 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 flavoring the solution by the pharmacist prior to dispensing, are examples of interventions that may improve tolerability.

Do Not Use Crushed Tablets

Ritonavir-boosted lopinavir 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.[30] In a PK study using a generic adult formulation of ritonavir-boosted lopinavir manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C_{trough} measurements.[21]

Toxicity

Weight Gain

Compared with children treated with NNRTI-based regimens, those treated with ritonavir-boosted lopinavir may have less robust weight gain and smaller increases in CD4 percentage.[31-33] The poor weight gain associated with ritonavir-boosted lopinavir 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 November 1, 2012; last reviewed February 12, 2014)

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

- 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)

- *Metabolism:* Cytochrome P (CYP) 2C19 and 3A4 substrate. Metabolized to active M8 metabolite. CYP3A4 inhibitor. However, ritonavir boosting does not significantly increase nelfinavir concentrations and co-administration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir.
- Before administering nelfinavir, carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- *More common:* Diarrhea (most common), asthenia, abdominal pain, rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NFV.html).

Pediatric Use

Approval

Nelfinavir is a protease inhibitor (PI) approved for use in combination with 2 nucleoside reverse transcriptase inhibitors in children aged >2 years. Nelfinavir is not recommended for treatment of children aged <2 years (see the Perinatal Guidelines).

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 combination antiretroviral therapy (cART), the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. 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.[9-11]

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. In the PENTA-7 trial, 35% (7 of 20) of infants started on powder at initiation of therapy were switched from the powder to crushed tablets because of difficulty administering the oral formulation to the infants.[1] 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.[12]

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 adults,[13] 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.[14,15] 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.[9]

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.[16-18]

The antiviral response to nelfinavir is significantly less in children younger than age 2 years than in older children.[6,8,19] Infants have even lower drug exposures and higher variability in plasma concentrations than children with body weights <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.[20,21] 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.[22] 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.[22] Therapeutic drug monitoring (TDM) of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir.[16,23] Similarly, better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing;[15,24] doses higher than those recommended in adults may be required in some patients. 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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Ritonavir (RTV, Norvir) (Last updated February 12, 2014; last reviewed February 12, 2014)

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:

- The major use of ritonavir is as a PK enhancer of other protease inhibitors (PIs) used in pediatric patients and in adolescents and adults. The recommended dose of ritonavir varies and is specific to the drug combination selected. See dosing information for specific PIs.

In the Unusual Situation When Ritonavir is Prescribed as Sole PI:

- See manufacturer guidelines.

Selected Adverse Events

- Gastrointestinal (GI) 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 GI side effects.
- 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 room temperature (68–77° F or 20–25° 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 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.

Metabolism

- Cytochrome P (CYP) 3A4 and CYP 2D6 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)

- *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.
- Avoid concomitant use of intranasal or inhaled fluticasone. Use caution when prescribing ritonavir with other inhaled steroids because of reports of adrenal insufficiency.[1]

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 pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.[2]

Resistance

Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic enhancer of other protease inhibitors (PIs).

Pediatric Use

Approval

Ritonavir has been approved by the Food and Drug Administration (FDA) for use in the pediatric population.

Efficacy: Effectiveness in Practice

Use of ritonavir as the sole PI in combination antiretroviral therapy (cART) in children is not recommended. Although ritonavir has been well studied in children, its use as a sole PI for therapy is limited because ritonavir is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. Also, ritonavir as a sole PI is associated with a higher risk of virologic failure than efavirenz or ritonavir-boosted lopinavir.[3-5] 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. Concentrations are highly variable in children younger than aged 2 years, and doses of 350 to 450 mg/m^2 twice daily may not be sufficient for long-term suppression of viral replication in this age group.[6-14] However, in both children and adults, ritonavir is recommended as a PK enhancer to boost the second PI in an ART regimen. Ritonavir acts by inhibiting the metabolism of the second (boosted) PI by the liver, thereby increasing the plasma concentration of the second (boosted) PI.

Dosing

Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, atazanavir and a PI co-formulation, ritonavir-boosted lopinavir, are available (see individual PIs for more specific information).

Toxicity

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily.[2] Potentially life-threatening arrhythmias in premature newborn infants treated with ritonavir-boosted lopinavir have been reported; thus, ritonavir-boosted lopinavir should not be used in this group of patients.[15,16] 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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Saquinavir (SQV, Invirase) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

Hard-Gel Capsules: 200 mg

Film-Coated Tablets: 500 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children.

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

Aged ≥7 Years in Combination with Ritonavir-Boosted Lopinavir for Salvage Therapy (Conditional Dosing Based On Limited Data, See Text):

- Saquinavir 750 mg/m^2 (max 1600 mg) and saquinavir 50 mg/kg each have been used in combination with ritonavir-boosted lopinavir, both twice daily.

Adolescent (Aged ≥16 years)/Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir or ritonavir-boosted lopinavir (never unboosted).
- Saquinavir 1000 mg + ritonavir 100 mg, both twice daily
- Saquinavir 1000 mg + ritonavir-boosted lopinavir 400/100 mg, both twice daily

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Increased bleeding episodes in patients with hemophilia
- PR interval prolongation, QT interval prolongation and ventricular tachycardia (torsades de pointes) have been reported.

Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram is recommended and saquinavir is contraindicated in patients with a prolonged QT interval.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate 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]())

- Saquinavir is both a substrate and inhibitor of the CYP3A4 system. Potential exists for multiple drug interactions. Co-administration of saquinavir is contraindicated with drugs that are highly dependent on the CYP3A clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, lipodystrophy.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and ventricular tachycardia (torsades de pointes).

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/SQV.html).

Pediatric Use

Approval

Saquinavir is not Food and Drug Administration (FDA)-approved for use in children.

Efficacy

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors in HIV-infected children.[1-6] Ritonavir-boosted saquinavir and saquinavir/lopinavir/ritonavir regimens were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications.[1,3-9]

Pharmacokinetics

Studies suggest that saquinavir should not be used without boosting by ritonavir or ritonavir-boosted lopinavir. A pharmacokinetic (PK) analysis of 5 children aged younger than 2 years and 13 children aged 2 to 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir 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 18 children (median age 14.2 years, range 7.7–17.6 years) evaluating the addition of saquinavir (750 mg/m^2 body surface area every 12 hours, maximum dose 1600 mg) to a regimen containing ritonavir-boosted lopinavir dosed at 400/100 mg/m^2 body surface area twice daily (for patients not concurrently taking a non-nucleoside reverse transcriptase inhibitor [NNRTI]) or ritonavir-boosted lopinavir 480/120 mg/m^2 body surface area twice daily for patients concurrently administered an NNRTI, the addition of saquinavir was well tolerated and did not appear to alter lopinavir PKs. Saquinavir required dose adjustment in four patients (decreased in three, increased in one).[9]

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance (saquinavir was dosed at 50 mg/m^2 body surface area and 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]

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. Ritonavir-boosted saquinavir is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval. An ECG is recommended before initiation of therapy with saquinavir and should be considered during therapy.

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Tipranavir (TPV, APTIVUS) (Last updated November 1, 2012; last reviewed February 12, 2014)

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 (PIs).

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 Dose:

- 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 Dose:

- 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°–46° F). Once bottle is opened, capsules can be kept at room temperature (maximum of 77° F or 25° C) if used within 60 days.
- Use tipranavir with caution in patients who may be at increased risk of intracranial

hemorrhage: risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, use of anticoagulant or antiplatelet agents (including vitamin E).

- Use of tipranavir is contraindicated in patients with moderate or severe hepatic impairment.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer and 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.)

- Tipranavir has the potential for multiple drug interactions. Co-administration of ritonavir-boosted tipranavir with drugs that are highly dependent on CYP3A for clearance or are potent CYP3A inducers is contraindicated.
- Before tipranavir is administrated, a patient's medication profile should be carefully reviewed for potential drug interactions.
- 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 pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of intracranial hemorrhage. Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TPV.html).

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 that limit its use to patients with few treatment options. However, tipranavir is approved for use in children as young as age 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 ritonavir-boosted tipranavir in HIV-infected children (PACTG 1051/BI-1182.14).[2] This study enrolled treatment-experienced children (with the exception of 3 treatment-naive patients) aged 2 to 18 years (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children in 3 age strata were randomized to 2 different doses of tipranavir/ritonavir: ritonavir-boosted tipranavir 290 mg/115 mg per m^2 body surface area (low dose, 58 patients) or 375 mg/150 mg/m^2 body surface area (high dose, 57 patients) twice daily, plus optimized background therapy. All children initially received the oral solution but patients who were aged 12 years or older and receiving the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily were eligible to switch to tipranavir capsules after Week 4. At baseline, resistance to all commercially available PIs was present in greater than 50% of patient isolates, and the ritonavir-boosted tipranavir mutation scores increased with age.[2] At 48 weeks, 39.7% of patients receiving the low dose and 45.6% of those receiving the high dose had viral loads <400 copies/mL. The groups did not differ in percentage of patients who achieved viral loads <50 copies/mL. HIV RNA levels <400 copies/mL tended to be seen in a greater proportion of the youngest patients (70%), who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 T lymphocyte count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively.

In a multivariate model, three variables (listed in order) predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100,000 copies/mL. GIQ is calculated by dividing the tipranavir trough concentration by the number of tipranavir resistance-conferring mutations genotyped from a patient's HIV strain. The GIQ was consistently greater in the high-dose group. Based on these findings and the increased number of AIDS-defining events in the low-dose group, high-dose ritonavir-boosted tipranavir has been recommended.

Pharmacokinetics

Pharmacokinetic evaluation of the liquid formulation at steady state in children was assessed.[3] In children aged 2 to <12 years, at a dosage of ritonavir-boosted tipranavir 290/115 mg/m^2 body surface area, tipranavir trough concentrations were consistent with those achieved in adults receiving standard ritonavir-boosted tipranavir 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 ritonavir-boosted tipranavir dose. Population PK analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age.[3] Based on these studies, the final dose of ritonavir-boosted tipranavir 375/150 mg/m^2 body surface area twice daily is recommended.

Toxicity

Adverse effects were similar between treatment groups in the multicenter, pediatric study.[2] Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs because of adverse events. The most common adverse events 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. Four patients (all in the low-dose group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus high-dose group reached statistical significance ($P = 0.04$).

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%.[4]

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Entry and Fusion Inhibitors

Enfuvirtide (ENF, T-20, Fuzeon)

Maraviroc (MVC, Selzentry)

Enfuvirtide (ENF, T-20, Fuzeon) (Last updated February 12, 2014; last reviewed February 12, 2014)

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 (90-mg strength), 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. Re-challenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of SQ injections. Enfuvirtide injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject enfuvirtide immediately or keep refrigerated in the original vial until use. Reconstituted enfuvirtide must be used within 24 hours.
- Enfuvirtide must be given SQ; severity of reactions increases if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions apply ice or heat after injection or gently massage injection site

to better disperse the dose. There are reports of injection-associated neuralgia and paresthesia when alternative delivery systems, such as needle-free injection devices, are used.

- Advise patient/caregiver of the possibility of a HSR; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a HSR.

Metabolism

- Catabolism to constituent amino acids.

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

- There are no known significant drug interactions with enfuvirtide.

Major Toxicities

- *More common:* Almost all patients (87%–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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/enfuvirtide.html).

Pediatric Use

Approval

Although enfuvirtide is Food and Drug Administration (FDA)-approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high rate of injection site reactions. Use in deep salvage regimens[3] has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).

Pharmacokinetics

A single-dose pharmacokinetic (PK) 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 Food and Drug Administration (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) 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 years 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 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 February 12, 2014; last reviewed February 12, 2014)

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 <16 years.
- A pediatric clinical trial is under way.

Adolescent (Aged ≥16 Years)/Adult Dose

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including protease inhibitors (except ritonavir-boosted tipranavir)	150 mg twice daily
When given with nucleoside reverse transcriptase inhibitors, enfuvirtide, ritonavir-boosted tipranavir, 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 main body of the 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

- 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 in patients with hepatic impairment may be increased.

- 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](#))

- *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 less 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

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html). 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 <16 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 of and follow up with participants in this trial continues.

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Integrase Inhibitors

Dolutegravir (DTG, Tivicay, GSK1349572)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

Dolutegravir (DTG, Tivicay, GSK1349572) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

Tablet: 50 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.

Children Aged ≥12 Years and Weighing At Least 40 kg (Treatment-Naive or Treatment-Experienced/ Integrase Strand Transfer Inhibitor [INSTI]-Naive):

- 50 mg once daily
- If co-administered with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin, then 50 mg twice daily should be given.

Adult Dose

Adult Population	Recommended Dose
Treatment-naive or treatment-experienced/INSTI-naive	50 mg once daily
Treatment-naive or treatment-experienced/ INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a]	50 mg twice daily

[a] Combinations that do not include metabolic inducers should be considered where possible.

Selected Adverse Events

- Insomnia
- Headache

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
- Poor virologic response to 50 mg dolutegravir twice daily may occur if INSTI-resistance Q148 substitution is present along with 2 or more additional INSTI-resistance mutations: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

Metabolism

- 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. Dolutegravir is not recommended in patients with severe hepatic impairment because of lack of data.
- Dosing in patients with renal impairment: No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment or in INSTI-experienced patients with mild or moderate renal impairment.
- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min)

because dolutegravir concentrations will be decreased (the cause of this decrease is unknown).

Drug Interactions:

- *Metabolism:* Dolutegravir is a UGT1A1 and CYP 3A substrate and may require dosage adjustments when administered with UGT1A1 or CYP 3A-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.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (http://www.iasusa.org/resistance_mutations/index.html), and the Stanford University HIV Drug Resistance database offers a discussion of integrase strand transfer inhibitor (INSTI) mutations (http://hivdb.stanford.edu/DR/INIResiNote.html). Poor virologic response to 50 mg dolutegravir twice daily may occur if INSTI-resistance Q148 substitution is present along with 2 or more additional INSTI-resistance mutations (see table above for list).

Pediatric Use

Approval

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other antiretroviral drugs for children aged 12 years and older, weighing at least 40 kg, and who are treatment-naive or treatment-experienced and INSTI-naive.

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. 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 comparable exposures to those seen in adults receiving 50 mg once daily.[1] 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 24 weeks, 70% had achieved HIV RNA concentration <50 copies/mL. No safety or tolerability concerns were identified.[2] 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). An oral pediatric granule formulation will also be studied.

References

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Elvitegravir (EVG) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

Formulations

Only available in a fixed-dose combination tablet (Stribild):

Elvitegravir (EVG) + cobicistat (COBI) + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF)

EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg

Dosing Recommendations

Pediatric Dose (aged <18 years):

- Not Food and Drug Administration (FDA)-approved or -recommended for use in children aged <18 years.

Adult Dose (aged ≥18 years):

- 1 tablet once daily in antiretroviral (ARV) treatment-naive adults.

Selected Adverse Events

- Diarrhea, nausea, flatulence
- Renal insufficiency
- Cobicistat alters tubular secretion of creatinine, and therefore, may decrease creatinine-based estimates of glomerular filtration rate without a true change in glomerular filtration.
- Decreased bone mineral density (BMD).

Special Instructions

- Administer with food.
- Monitor estimated creatinine clearance, urine glucose, and urine protein; 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 FTC or TDF. Severe acute exacerbation of HBV can occur when FTC or TDF are discontinued; therefore, monitor hepatic function for several months after therapy with FTC or TDF is stopped.
- Not recommended for use with other ARV drugs.

Metabolism

- 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.
- Stribild should not 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])

- *Metabolism:* Stribild contains elvitegravir and cobicistat. Elvitegravir is metabolized by cytochrome P (CYP) 3A4 and is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, it inhibits ATP-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided.
- *Protease inhibitors:* Stribild should not be administered concurrent with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A.
- Not recommended for use with other ARV drugs.

Major Toxicities

- *More common:* Nausea, diarrhea, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors including tenofovir disoproxil fumarate (tenofovir) and emtricitabine. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking tenofovir; 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. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

Pediatric Use

Approval

Elvitegravir is only available as the fixed-dose combination product Stribild, which contains elvitegravir/cobicistat/emtricitabine/tenofovir. Stribild is not FDA-approved for use in children aged <18 years. There are currently no data on its use in individuals aged <18 years, although studies in participants as young as age 12 years are ongoing.

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor added as a pharmacokinetic enhancer. Cobicistat slows elvitegravir metabolism and allows once-daily administration of the combination. Stribild is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive adults aged ≥18 years[1] based on trials showing non-inferiority to regimens of emtricitabine/tenofovir plus atazanavir/ritonavir,[2,3] or emtricitabine/tenofovir plus efavirenz.[4,5] There is cross-resistance between elvitegravir and raltegravir.[6] Cobicistat alters the renal tubular secretion of creatinine, so creatinine-based calculations of estimated glomerular filtration rate (eGFR) will be altered, even though the actual GFR might be only minimally changed.[7] Adults who experience a confirmed increase in serum creatinine greater than 0.4 mg/dL from baseline should be closely monitored for renal toxicity by following creatinine for further increases and urinalysis for evidence of proteinuria or glycosuria.[1]

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Raltegravir (RAL, Isentress) (Last updated February 12, 2014; last reviewed February 12, 2014)

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

For Oral Suspension: Single-use packet of 100 mg (expected fall 2014)

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 UGT1A1 is immature in neonates. Neonatal dose will be studied in full-term infants in IMPAACT P1110.

Infant/Pediatric Dose

Oral Suspension Dosing Table[a]

Children at least 4 weeks of age 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 for chewable tablet dose.

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Can be given without regard to food.
- Chewable tablets may be chewed or swallowed whole.
- **Film-coated tablets, chewable tablets, and oral suspension are not interchangeable.** Chewable tablets and oral suspension have better bioavailability than the film-coated tablets.
- 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 which includes 2 mixing cups, 2 dosing syringes, and 60 foil packets. Detailed instructions are provided in 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

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

within 30 minutes of mixing; unused solution should be discarded as directed in Instructions for Use document

Metabolism

- Uridine diphosphate glucotransferase (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.)

- *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.
- In adults, an increased dose of raltegravir is recommended when co-administered with rifampin. The appropriate dose adjustment is not known in children.
- Efavirenz and etravirine may decrease raltegravir concentrations.
- 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 2 hours of aluminum and/or magnesium hydroxide-containing antacids resulted in significantly reduced raltegravir plasma levels and is not recommended.

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 coinfected.

- *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, especially in those with prior history. Rash including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis have been reported. Thrombocytopenia.

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/INIResiNote.html).

Pediatric Use

Approval

Raltegravir is FDA-approved for use in infants and children aged ≥ 4 weeks and weight ≥3 kg. Current pediatric 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

Children Aged 2 to 18 Years

IMPAACT P1066 is a Phase I/II open label multicenter study to evaluate the pharmacokinetic (PK) profile, safety, tolerability, and efficacy of various formulations of raltegravir in combination antiretroviral treatment (cART)-experienced, HIV-infected children and adolescents aged 2 to 18 years in combination with an optimized background cART regimen.[2] Subjects receive 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 includes intensive PK evaluation in various age cohorts: (aged 12 to <19 years, 6 to <12 years, 2 to <6 years). Dose selection is based upon achieving target PK parameters similar to those seen in adults: PK targets are geometric mean (GM) area under the curve of 14–25 μMxh and GM 12-hour concentration >33 nM. Additional subjects are then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. Ninety-three (97%) subjects completed 24 weeks of treatment with 54% achieving HIV RNA <50 copies/mL with a mean CD4 T lymphocyte (CD4) count (percent [%]) increase of 119 cells/mm^3 (3.8%). Ninety-one subjects completed 48 weeks of treatment with 57% achieving HIV RNA <50 copies/mL with a mean CD4 count (percent [%]) increase of 156 cells/mm^3 (4.6%).[2] In subjects who experienced virologic failure, development of drug resistance and/or poor adherence were contributing factors. The frequency, type, and severity of drug-related adverse reactions through week 48 were comparable to those observed in adult studies. Observed adverse reactions considered drug-related included one patient with grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; one patient with a grade 2 allergic rash; and one patient with grade 3 ALT and grade 4 AST laboratory elevations. There were no discontinuations due to adverse events and no drug-related deaths.

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.[3] Additional experience from the French expanded access program in treatment-experienced adolescents support the good virologic and immunologic results observed in P1066.[4,5]

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 oral suspension in combination with an optimized background regimen. All subjects had received prior antiretrovirals 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. Twenty-three (88%) completed 48 weeks of treatment with 44% achieving HIV RNA <50 copies/mL with a mean CD4 cell count (percent [%]) increase of

492 cells/mm^3 (7.8%).[1] PK parameters were similar to those achieved for the older cohorts in P1066.

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.[6]

Washout PK of raltegravir in neonates born to HIV-infected pregnant women was studied in P1097.[7] 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 that will evaluate the safety and PK of raltegravir in HIV-1 exposed neonates at high risk of acquiring HIV-1 infection.

Formulations

The PK of raltegravir were 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.[8]

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.[9] Interpatient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.[1,10] Because of the differences in the bioavailability of the chewable and film-coated tablets, the dosing recommendations are different and these products are **not interchangeable**.

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Appendix B: Acronyms (Last updated February 12, 2014; last reviewed February 12, 2014)

Acronym/Abbreviation	Full Name
3TC	lamivudine
AAP	American Academy of Pediatrics
ABC	abacavir
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
BUN	blood urea nitrogen
cART	combination antiretroviral therapy
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CHER Trial	The Children with HIV Early Antiretroviral Therapy Trial
CHIPS	Collaborative HIV Pediatric Study
CK	creatine kinase
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
COBI	cobicistat
CPK	creatine phosphokinase
CrCl	creatinine clearance
CT	computed tomography

CVD	cardiovascular disease
CYP	cytochrome P
D/M	dual-mixed (tropic)
d4T	stavudine
ddI	didanosine
DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetate
DOT	directly observed therapy
DRESS	drug rash with eosinophilia and systemic symptoms
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DXA	dual-energy x-ray absorptiometry
EBV	Epstein-Barr virus
EC	enteric-coated
ECG	electrocardiogram
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
EM	erythema multiforme
ENV, ENF	enfuvirtide
ETR, ETV	etravirine
EVG	elvitegravir
FDA	Food and Drug Administration
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
GGT	gamma glutamyl transpeptidase
GI	gastrointestinal
GIQ	genotypic inhibitory quotient
HAART	highly active antiretroviral therapy

HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
HHS	U.S. Department of Health and Human Services
HIVMA	HIV Medicine Association
HPPMCS	HIV Paediatric Prognostic Markers Collaborative Study
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
HSV	herpes simplex virus
IAS-USA	International Antiviral Society-USA
IC_{50}	mean inhibitory concentration
ICH	intracranial hemorrhage
IDSA	Infectious Diseases Society of America
IDV	indinavir
IFA assay	immunofluorescent antibody assay
IgE	immunoglobulin E
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRIS	immune reconstitution inflammatory syndrome
IU	international units
IUD	intrauterine device
IV	intravenous/intravenously
IVIG	intravenous immune globulin
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LIP	lymphoid interstitial pneumonia
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir
MAC	*Mycobacterium avium* complex

m-DOT	modified directly observed therapy
MEMS	Medication Event Monitoring System
MRI	magnetic resonance imaging
msec	milliseconds
MVC	maraviroc
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor/non-nucleoside analogue reverse transcriptase inhibitor
non-HDL-C	non-high-density lipoprotein cholesterol
NRTI	nucleoside reverse transcriptase inhibitor/nucleoside analogue reverse transcriptase inhibitor
NVP	nevirapine
OARAC	Office of AIDS Research Advisory Council
OBR	optimized background regimen
OBT	optimized background therapy
OGTT	oral glucose tolerance test
OI	opportunistic infection
PBMC	peripheral blood mononuclear cells
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PENTA	Paediatric European Network for Treatment of AIDS
PG	plasma glucose
Pgp	p-glycoprotein
PI	protease inhibitor
PIDS	Pediatric Infectious Diseases Society
PK	pharmacokinetic
PPI	proton-pump inhibitor
PR	protease
PUFA	polyunsaturated fatty acid
RAL	raltegravir
RBV	ribavirin
RPG	random plasma glucose

RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SJS	Stevens-Johnson syndrome
SQ	subcutaneous
SQV	saquinavir
STI	structured treatment interruptions
T-20	enfuvirtide
TB	tuberculosis
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrolysis
TG	triglyceride
THAM	tris–hydroxymethyl-aminomethane
TMP-SMX	trimethoprim sulfamethoxazole
TPV	tipranavir
TPV/r	ritonavir-boosted tipranavir
UA	urinalysis
UGT1A1	uridine diphosphate glucoronosyltransferase
ULN	upper limit of normal
USPHS	U.S. Public Health Service
WHO	World Health Organization
ZDV	zidovudine

Appendix C: Supplemental Information (Last updated February 12, 2014; last reviewed February 12, 2014)

Table A. Likelihood of Developing AIDS or Death Within 12 Months, by Age and CD4 T-Cell Percentage or Log_{10} HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

	CD4 Percentage				Log_{10} HIV RNA Copy Number		
Age	**10%**	**20%**	**25%**	**30%**	**6.0**	**5.0**	**4.0**
Percent Mortality (95% Confidence Interval)							
6 Months	28.7	12.4	8.5	6.4	9.7	4.1	2.7
1 Year	19.5	6.8	4.5	3.3	8.8	3.1	1.7
2 Years	11.7	3.1	2.0	1.5	8.2	2.5	1.1
5 Years	4.9	0.9	0.6	0.5	7.8	2.1	0.7
10 Years	2.1	0.3	0.2	0.2	7.7	2.0	0.6
Percent Developing AIDS (95% Confidence Interval)							
6 Months	51.4	31.2	24.9	20.5	23.7	13.6	10.9
1 Year	40.5	20.9	15.9	12.8	20.9	10.5	7.8
2 Years	28.6	12.0	8.8	7.2	18.8	8.1	5.3
5 Years	14.7	4.7	3.7	3.1	17.0	6.0	3.2
10 Years	7.4	2.2	1.9	1.8	16.2	5.1	2.2

Note: Table modified from: HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet*. 2003;362:1605-1611.

Table B. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Cell Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)

Age (Years)	Absolute CD4 Cell Count (cells/mm^3)					
	<50	**50–99**	**100–199**	**200–349**	**350–499**	**500+**
Rate of Death Per 100 Patient-Years						
0–4	59.3	39.6	25.4	11.1	10.0	3.5
5–14	28.9	11.8	4.3	0.89	0.00	0.00
15–24	34.7	6.1	1.1	0.71	0.58	0.65
25–34	47.7	10.8	3.7	1.1	0.38	0.22
35–44	58.8	15.6	4.5	0.92	0.74	0.85
45–54	66.0	18.8	7.7	1.8	1.3	0.86
55+	91.3	21.4	17.6	3.8	2.5	0.91
Rate of AIDS or Death per 100 Patient-Years						
0–4	82.4	83.2	57.3	21.4	20.7	14.5
5–14	64.3	19.6	16.0	6.1	4.4	3.5
15–24	61.7	30.2	5.9	2.6	1.8	1.2
25–34	93.2	57.6	19.3	6.1	2.3	1.1
35–44	88.1	58.7	25.5	6.6	4.0	1.9
45–54	129.1	56.2	24.7	7.7	3.1	2.7
55+	157.9	42.5	30.0	10.0	5.1	1.8

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

Table C. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4 T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children[a]

Baseline HIV RNA[c] (Copies/mL) Baseline CD4 Percentage	No. Patients[d]	Deaths[b] Number	Deaths[b] Percentage
≤100,000			
≥15%	103	15	(15%)
<15%	24	15	(63%)
>100,000			
≥15%	89	32	(36%)
<15%	36	29	(81%)

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

[b] Mean follow-up: 5.1 years.

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

[d] Mean age: 3.4 years.

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

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

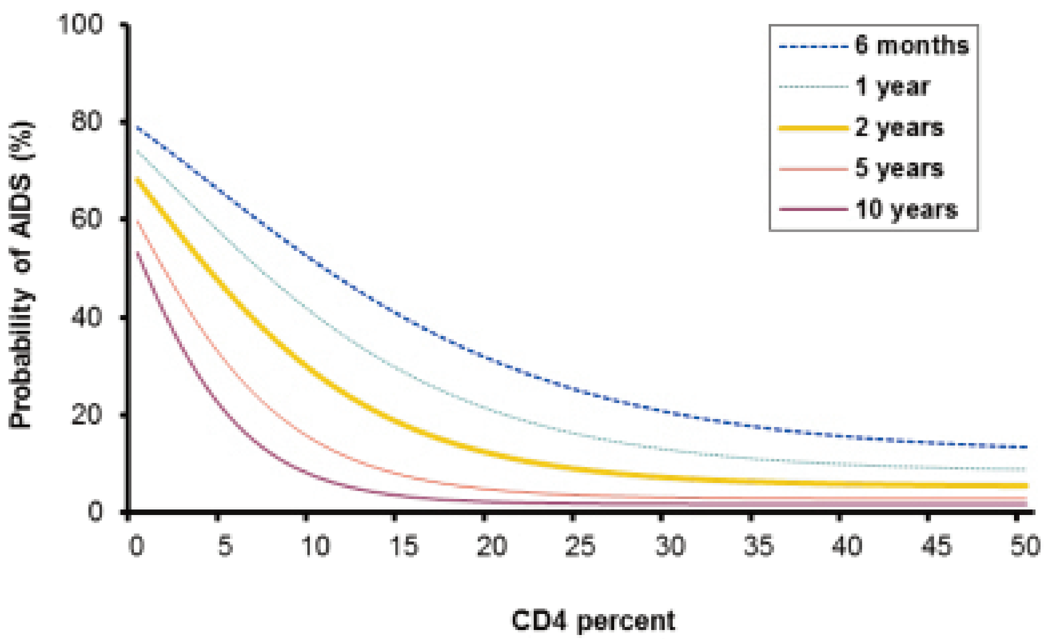

Figure modified from *Lancet* 2003;362:1605-1611

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

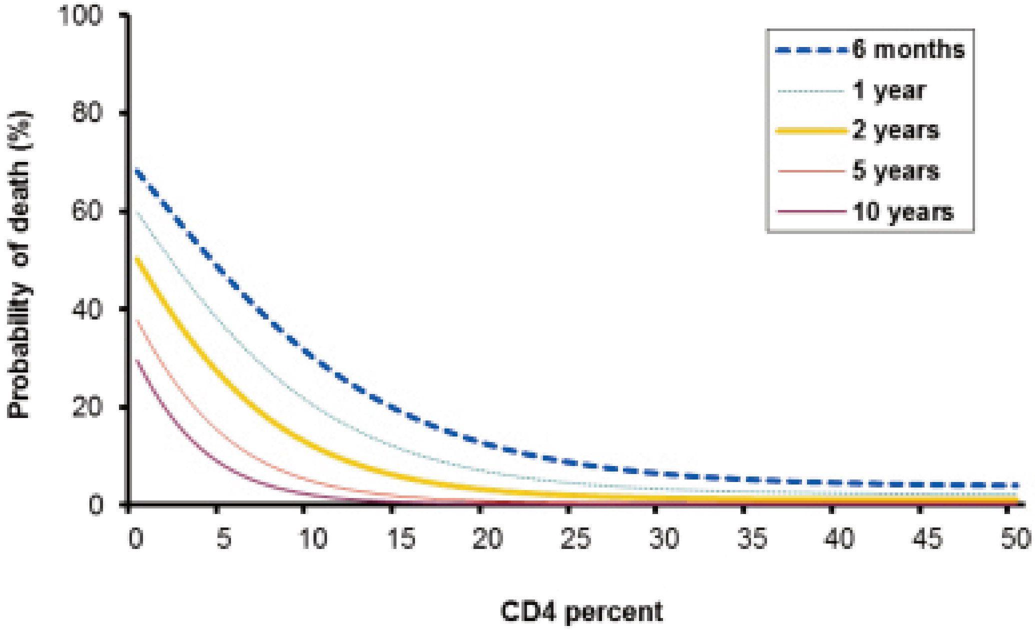

Figure modified from *Lancet* 2003;362:1605-1611

Figure C. Death Rate per 100 Person-Years in HIV-Infected Children Aged 5 Years or Older in the HIV Paediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study*

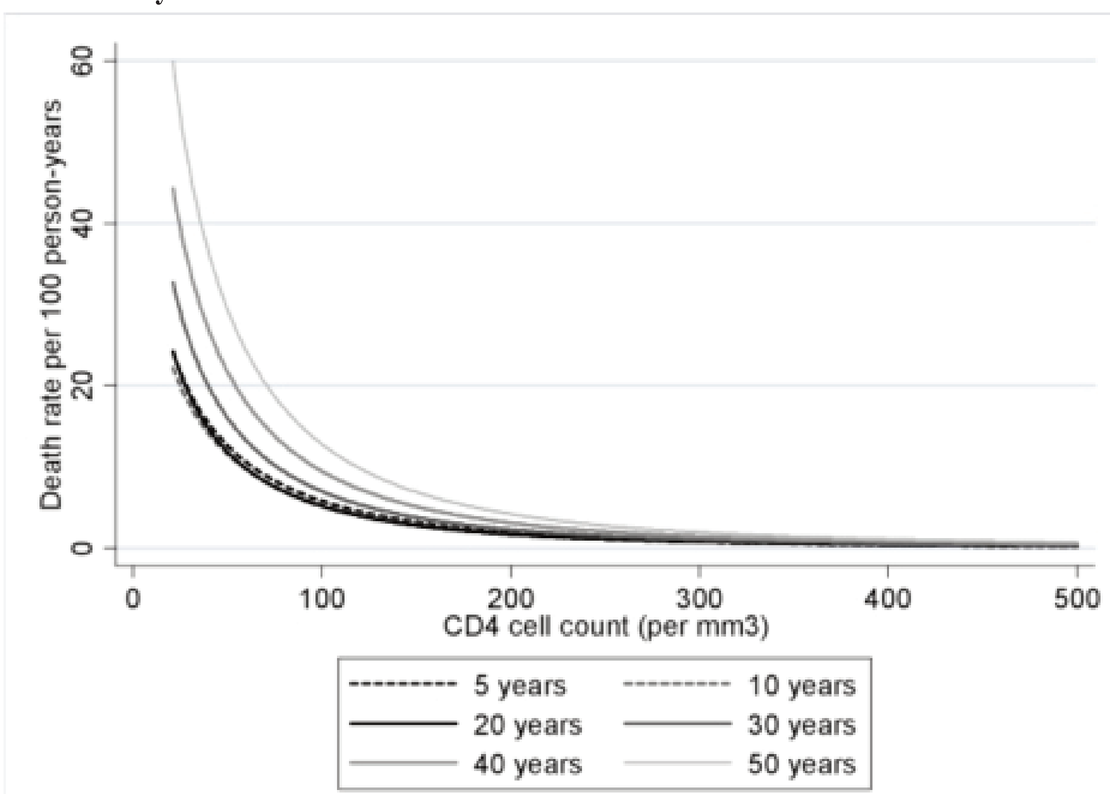

Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis*. 2008;197:398-404.

Figure D. Estimated Probability of AIDS Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

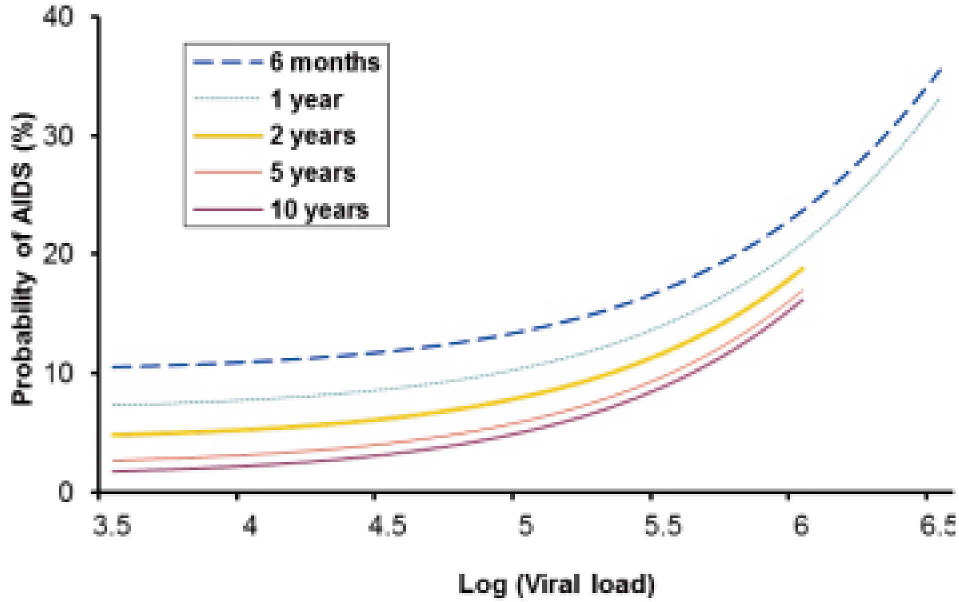

Figure modified from *Lancet* 2003;362:1605-1611

Figure E. Estimated Probability of Death Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

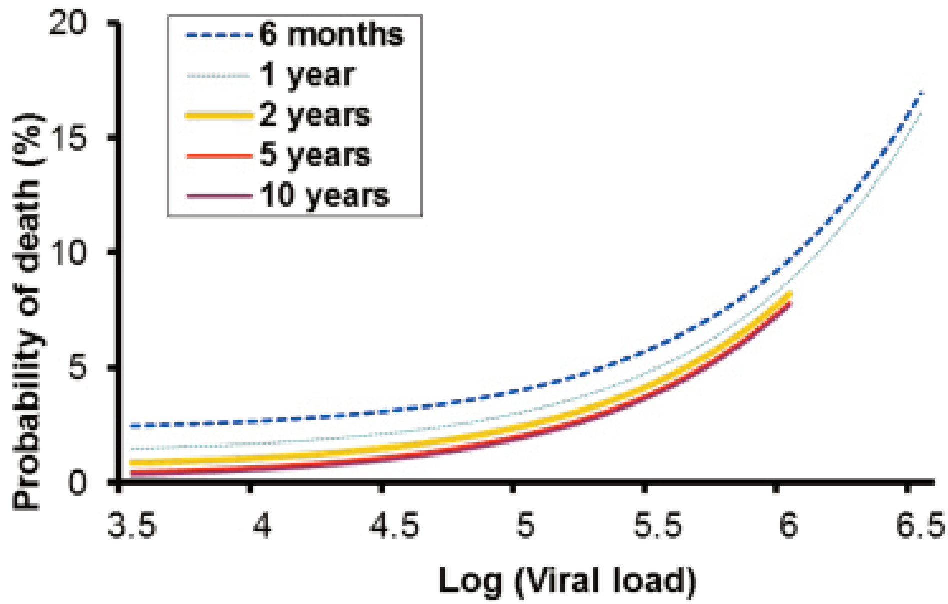

Figure modified from *Lancet* 2003;362:1605-1611