Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Identification of Perinatal HIV Exposure (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.
• Repeat HIV testing in the third trimester, before 36 weeks' gestation, should be considered for all HIV-seronegative pregnant women and is recommended for pregnant women who are at high risk of HIV infection **(AIII)**.
• 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 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 antibody testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing. If results in mother or infant are positive, infant antiretroviral prophylaxis should be initiated immediately and the mothers should not breastfeed unless confirmatory HIV antibody testing is negative **(AII)**. In infants with initial positive HIV viral tests (RNA, DNA), prophylaxis should be stopped and antiretroviral treatment initiated.
• 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

Diagnosis of HIV Infection in Infants and Children (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months; antibody tests should not be used **(AII)**.
• HIV RNA and HIV DNA nucleic acid tests (NATs) 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 **(AIII)**.
• 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 two or more negative virologic tests, with one obtained at age ≥1 month and one at age ≥4 months, or two 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)**.
• Children with perinatal HIV exposure aged 18 to 24 months may have residual maternal HIV antibodies; definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on a NAT (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations) **(AII)**.
• Diagnosis of HIV infection in children with non-perinatal exposure or children with perinatal exposure aged >24 months relies primarily on the use of HIV antibody tests; when acute HIV infection is suspected, testing with an HIV NAT may be necessary to diagnose HIV infection **(AII)**.

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Clinical and Laboratory Monitoring of Pediatric HIV Infection

(Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• Absolute CD4 T lymphocyte (CD4) cell count is recommended for monitoring immune status in children of all ages, with CD4 percentage as an alternative **(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 and plasma viral load monitoring should be implemented 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 to 4 weeks after treatment initiation **(AIII)**.
• Children on cART should have therapy adherence, effectiveness (by CD4 cell count/percentage and plasma viral load), and toxicities (by history, physical, and selected laboratory tests) routinely 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*
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Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive, HIV-Infected Infants and Children

Panel Recommendations	
Recommend Urgent Treatment[a]	Combination Antiretroviral Therapy (cART) Should Be Initiated Urgently in All HIV-Infected Children with any of the Following: *Age <12 Months:* • **AI** for infants age <12 weeks • **AII** for infants 12 weeks–12 months *CDC Stage 3* ***(AI*)****:* • Aged 1 to <6 years, CD4 count[c] <500 cells/mm^3 • Aged ≥ 6 years,[c] CD4 count <200 cells/mm^3
Recommend Treatment[b]	cART Should Be Initiated in HIV-Infected Children Aged ≥1 Year with any of the Following: • Moderate HIV-related symptoms **(AII)** (see Table 7) • Plasma HIV RNA >100,000 copies/mL[d] **(AII)** *CDC Stage 2:* • Age 1 to <6 years,[c] CD4 count 500–999 cells/mm^3 **(AII)** • Age ≥6 years,[c] CD4 count 200–499 cells/mm^3 (**AI*** if CD4 count <350 cells/mm^3; **AII*** if CD4 count 350–499 cells/mm^3)
Consider Treatment[b]	cART Should Be Considered for HIV-Infected Children Aged ≥1 Year with: • Mild HIV-related symptoms (see Table 7) or asymptomatic **and** *CDC Stage 1 (see Table 6):* • Ages 1 to <6 years,[c] CD4 count ≥1000 cells/mm^3 **(BIII)** • Age ≥6 years,[c] CD4 count ≥ 500 cells/mm^3 **(BIII)**
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion † Studies that include children or children and adolescents but not studies limited to postpubertal adolescents	

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

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

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

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

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

What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.

• 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 backbone combination:
  ○ For neonates/infants aged ≥42 weeks postmenstrual **and** ≥14 days postnatal and children <3 years: lopinavir/ritonavir **(AI)**;
  ○ For children aged 3 years to <6 years: efavirenz or lopinavir/ritonavir **(AI*)**;
  ○ For children aged ≥6 years: atazanavir/ritonavir or efavirenz or lopinavir/ritonavir **(AI*)**.

• The Panel recommends the following preferred dual-nucleoside reverse transcriptase inhibitor backbone combinations:
  ○ For infants <3 months: 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 children aged ≥12 years: abacavir plus lamivudine or plus emtricitabine **(AI)**.
  ○ For adolescents at Tanner Stage 4 or 5: abacavir plus lamivudine or plus emtricitabine **(AI)** or tenofovir disoproxil fumarate plus lamivudine or plus emtricitabine **(AI*)**.

• Table 8 provides a list of Panel-recommended alternative and acceptable regimens.
• For infants aged <42 weeks postmenstrual or <14 days postnatal, data are currently inadequate to provide recommended dosing to allow the formulation of an effective, complete cART regimen (see Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection).
• Both emtricitabine and lamivudine, and tenofovir disoproxil fumarate have antiviral activity and efficacy against hepatitis B. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, the reader should access the 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*
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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• Combination antiretroviral therapy regimens must be individually tailored to the adolescent **(AIII)**.
• Reproductive options including preconception care, contraception methods, and safer sex techniques for prevention of secondary HIV transmission to sexual partners should be discussed regularly **(AI)**.
• Adolescents who are considering a planned pregnancy should be receiving a maximally suppressive combination antiretroviral therapy regimen **(AII)**.
• Providers should be aware of potential interactions between combination antiretroviral therapy and hormonal contraceptives that could lower contraceptive efficacy **(AII*)**.
• Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*
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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of combination antiretroviral therapy and again before changing regimens **(AIII)**. • Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**. • At least one method of measuring adherence to combination antiretroviral therapy should be used in addition to monitoring viral load **(AII)**. • When feasible, a once-daily antiretroviral regimen should be considered **(BI*)**. • 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*

Management of Medication Toxicity or Intolerance (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• In children who have severe or life-threatening toxicity, all antiretroviral drugs should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of a different antiretroviral drug or drugs for the offending agent(s) **(AII*)**. • When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen **(AI*)**. • The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity **(AIII)**. • Dose reduction is not a recommended option for management of ARV toxicity, except for those few antiretroviral drugs for which a therapeutic range of plasma concentrations detected by therapeutic drug monitoring correlates with toxicity **(AII*)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Management of Children Receiving Antiretroviral Therapy (Last updated March 5, 2015; last reviewed March 5, 2015)

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

Panel's Recommendations
• For children who have sustained virologic suppression on their current regimen, changing to a new antiretroviral regimen can be considered in order to facilitate adherence, decrease drug-associated toxicities, or improve safety **(BII)**.
• It is critical to consider past episodes of antiretroviral treatment failure, tolerability, and all prior drug resistance testing results to avoid choosing new ARV drugs for which archived drug resistance would limit activity.

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*

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Recognizing and Managing Antiretroviral Treatment Failure (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations

- The causes of virologic treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions—should be assessed and addressed **(AII)**.
- Perform antiretroviral (ARV) drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen **(AI*)**.
- 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 by or in collaboration with a pediatric HIV specialist **(AI*)**.

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

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Considerations About Interruptions in Antiretroviral Therapy (Last updated March 5, 2015, last reviewed March 5, 2015)

Panel's Recommendations

- Outside the context of clinical trials, structured interruptions of combination antiretroviral therapy are not recommended for children **(AIII)**.

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Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations

• Evaluation of plasma concentrations of antiretroviral drugs is 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);
  ○ 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 because the dosing recommendation depends on the result, given the significant association between this polymorphism and efavirenz concentrations **(AII)**.

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Antiretroviral Drug-Resistance Testing (Last updated March 5, 2015; last reviewed March 5, 2015)

Panel's Recommendations
• Antiretroviral drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment-naive patients **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**. • Antiretroviral drug resistance testing is recommended before changing therapy because of virologic 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 antiretroviral therapy regimens **(BIII)**. • The absence of detectable resistance to a drug does not ensure that use of the drug will be successful as mutations may not be detected once the drug has been discontinued. A history of all previously used antiretroviral agents and available resistance test results must be reviewed when making decisions regarding the choice of new agents **(AII)**. • Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered **(AI*)**. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist **(AI*)**. • Consultation with a pediatric HIV specialist is recommended for interpretation of resistance assays when considering starting or changing an antiretroviral 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*