Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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

Panel's Recommendations
• HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.
• Repeat HIV testing in the third trimester, before 36 weeks' gestation, should be considered for all HIV-seronegative pregnant women and is recommended for pregnant women who are at high risk of HIV infection **(AIII)**.
• Expedited HIV testing at the time of labor or delivery should be performed for any woman with undocumented HIV status; testing should be available 24 hours a day, and results available within 1 hour. If results are positive, intrapartum and infant postnatal antiretroviral (ARV) drug prophylaxis should be initiated immediately, pending results of supplemental HIV testing **(AII)**.
• Women who have not been tested for HIV before or during labor should undergo expedited HIV antibody testing during the immediate postpartum period or their newborns should undergo expedited HIV antibody testing. If results in mother or infant are positive, infant ARV drug prophylaxis should be initiated immediately, and the mothers should not breastfeed unless supplemental HIV testing is negative **(AII)**. In infants with initial positive HIV viral tests (RNA, DNA), prophylaxis should be stopped and antiretroviral therapy initiated.
• When acute HIV infection is suspected during pregnancy, in the intrapartum period, or while breastfeeding, initial testing should be performed with an antigen/antibody combination immunoassay; if the initial testing was performed with an HIV antibody test or supplemental testing is negative, an additional virologic test (RNA, DNA) may be necessary to diagnose HIV infection **(AII)**.
• Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
• Infant HIV antibody testing to determine HIV exposure should be considered for infants in foster care and adoptees for whom maternal HIV infection status is unknown **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*
† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Diagnosis of HIV Infection in Infants and Children (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations
• Virologic assays that directly detect HIV must be used to diagnose HIV infection in children younger than 18 months with perinatal HIV exposure; HIV antibody tests should not be used **(AII)**.
• HIV RNA and HIV DNA nucleic acid tests are recommended as preferred virologic assays **(AII)**.
• Virologic diagnostic testing at birth should be considered for HIV-exposed infants at high risk of perinatal HIV transmission **(AIII)**.

• Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:
  • 14 to 21 days **(AII)**
  • 1 to 2 months **(AII)** (preferably, 2 to 4 weeks after cessation of antiretroviral prophylaxis **[BIII]**)
  • 4 to 6 months **(AII)**.

• A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
• Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with 1 obtained at age ≥1 month and 1 at age ≥4 months, or 2 negative HIV antibody tests from separate specimens obtained at age ≥6 months **(AII)**.
• Some experts confirm the absence of HIV infection at 12 to 18 months of age in children with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.
• Children aged 18 to 24 months with perinatal HIV exposure may have residual maternal HIV antibodies; definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on a nucleic acid test (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations) **(AII)**.
• Diagnostic testing in children with non-perinatal exposure or children with perinatal exposure aged >24 months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV nucleic acid test may be necessary to diagnose HIV infection **(AII)**.
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Clinical and Laboratory Monitoring of Pediatric HIV Infection

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

Panel's Recommendations
• Absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of diagnosis of HIV infection and, if a child is not started on antiretroviral therapy (ART) after diagnosis, monitoring should be at least every 3 to 4 months thereafter **(AIII)**.
• Antiretroviral drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment naive patients **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**.
• After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical side effects and to support treatment adherence within 1 to 2 weeks, with laboratory testing for toxicity and viral load response recommended at 2 to 4 weeks after treatment initiation **(AIII)**.
• Children on ART should be monitored for therapy adherence, effectiveness (by CD4 cell count and plasma viral load), and toxicities (by history, physical, and selected laboratory tests) routinely (every 3 to 4 months) for the first 2 years **(AII*)**.
• More frequent CD4 cell count and plasma viral load monitoring should be performed in children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value **(AIII)**.
• CD4 cell count can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years **(AII)**.
• Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive antiretroviral therapy regimens **(BIII)**.
• The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, as mutations may not be detected once the drug has been discontinued. A history of all previously used antiretroviral agents and available resistance test results must be reviewed when making decisions regarding the choice of new agents **(AII)**.
• Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered **(AI*)**. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist **(AI*)**.
• Absolute CD4 cell count is recommended for monitoring immune status in children of all ages, with CD4 percentage as an alternative for children aged <5 years **(AII)**.

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

Panel Recommendations		
Age	**Criteria**	**Recommendation**
<12 Months[a]	Regardless of clinical symptoms, immune status, or viral load	Urgent[b] treatment (**All except AI** for ≥6 weeks to <12 weeks of age)
1 to <6 Years	CDC Stage 3-defining opportunistic illnesses[c]	Urgent[b] treatment **(AI*)**
	CDC Stage 3 immunodeficiency:[d] CD4 <500 cells/mm^3	
	Moderate HIV-related symptoms[c]	Treat[e] **(AII)**
	CD4 cell count[c] 500–999 cells/mm^3	
	Asymptomatic or mild symptoms[c] **and** CD4 cell count[c] ≥1000 cells/mm^3	Treat[e] **(BI*)**
≥6 Years	CDC Stage 3-defining opportunistic illnesses[c]	Urgent[a] treatment **(AI*)**
	CDC Stage 3 immunodeficiency:[d] CD4 <200 cells/mm^3	
	Moderate HIV-related symptoms[c]	Treat[b] **(AII)**
	CD4 cell count[d] 200–499 cells/mm^3	
	Asymptomatic or mild symptoms[c] **and** CD4 cell count ≥500 cells/mm^3	Treat[e] **(BI*)**

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

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

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

[c] Table 6

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

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

What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations
• Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.
• For treatment-naive children, the Panel recommends initiating antiretroviral therapy with three drugs, including either a boosted protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone.
• Table 7 provides a list of Panel-recommended regimens that are "Preferred," "Alternative" or for "Use in Special Circumstances;" recommendations vary by age, weight, and sexual maturity rating.
• For infants aged <42 weeks postmenstrual or <14 days postnatal, data are currently inadequate to provide recommended dosing to allow the formulation of an effective, complete antiretroviral therapy regimen (see Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection).
• Emtricitabine, lamivudine, and tenofovir disoproxil fumarate have antiviral activity and efficacy against hepatitis B. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, the reader should access the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children.
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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Last updated March 1, 2016; last reviewed March 1, 2016)

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

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

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

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy and again before changing regimens **(AIII)**.
• Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**.
• At least one method of measuring adherence to antiretroviral therapy should be used in addition to monitoring viral load **(AIII)**.
• Once-daily antiretroviral regimens and regimens with low pill burden should be prescribed whenever feasible **(AII*)**.
• To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care **(AII*)**.
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Management of Medication Toxicity or Intolerance (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Management of Children Receiving Antiretroviral Therapy (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Panel's Recommendations
• For children who have sustained virologic suppression on their current regimen, changing to a new antiretroviral regimen can be considered in order to facilitate adherence, simplify antiretroviral administration, increase antiretroviral potency, decrease drug-associated toxicities, or improve safety **(BII)**. • Past episodes of antiretroviral treatment failure, tolerability, and all prior drug resistance testing results should be considered in order to avoid choosing new ARV drugs for which archived drug resistance would limit activity **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*
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Recognizing and Managing Antiretroviral Treatment Failure (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations
• The causes of virologic treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions—should be assessed and addressed **(AII)**. • Perform antiretroviral drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen **(AI*)**. • Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*)**. • The new regimen should include at least two, but preferably three, fully active antiretroviral medications with assessment of anticipated antiretroviral activity based on past treatment history and resistance test results **(AII*)**. • The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay **(AI*)**. • When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future antiretroviral options **(AII)**. • Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist **(AI*)**.
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Considerations About Interruptions in Antiretroviral Therapy (Last updated March 1, 2016, last reviewed March 1, 2016)

Panel's Recommendations
• Outside the context of clinical trials, structured interruptions of antiretroviral therapy are not recommended for children **(AII)**.
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Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

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

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