



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

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# Maternal HIV Testing and Identification of Perinatal HIV Exposure (Last updated November 15, 2017; last reviewed November 15, 2017)

## Panel's Recommendations

- HIV testing is recommended as standard of care for all sexually active women, and should be a routine component of preconception care **(AII)**.
- All pregnant HIV-negative women in the United States should be tested as early as possible during each pregnancy **(AII)**.
- Repeat HIV testing in the third trimester is recommended for pregnant women with initial negative HIV antibody tests who are known to be at risk of acquiring HIV, who are receiving care in facilities that have an HIV incidence in pregnant women of at least 1 per 1,000 per year, who are incarcerated, or who reside in jurisdictions with elevated HIV incidence (see [Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings](#) and <http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf>) **(AII)**.
- 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 **(AII)**. If results are positive, intrapartum and infant postnatal antiretroviral (ARV) drug prophylaxis should be initiated immediately, pending results of supplemental HIV testing **(AII)** see [Perinatal Guidelines](#) for guidance.
- 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) **(AII)**. If results in mother or infant are positive, an appropriate infant antiretroviral (ARV) drug regimen should be initiated immediately, and the mothers should not breastfeed unless supplemental HIV testing is negative **(AII)**. Infants with initial positive HIV viral tests (RNA, DNA) should have their ARV regimen modified, if necessary, to a three-drug combination of ARV drugs at treatment dosages (antiretroviral therapy) (see [Antiretroviral Management of Exposed Infants](#)) **(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)**.
- HIV testing to determine HIV status is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown **(AIII)**.

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

**Rating of Evidence:** I = One or more randomized trials in children<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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# Diagnosis of HIV Infection in Infants and Children (Last updated November 15, 2017; last reviewed November 15, 2017)

## Panel's Recommendations

- Virologic assays (i.e., HIV RNA and HIV DNA nucleic acid tests) that directly detect HIV must be used to diagnose HIV infection in infants and children younger than 18 months with perinatal and postnatal HIV exposure; HIV antibody tests should not be used (AII).
- RNA or DNA polymerase chain reaction (PCR) testing are recommended equally for most patients; RNA PCR is recommended for known maternal non-subtype B virus (AII).
- 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)
  - 4 to 6 months (AII)
- Additional virologic diagnostic testing at birth should be considered for infants at higher risk of perinatal HIV transmission (AIII) and at 2 to 4 weeks after cessation of antiretroviral 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 1 obtained at age  $\geq 1$  month and 1 at age  $\geq 4$  months, or 2 negative HIV antibody tests from separate specimens obtained at age  $\geq 6$  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 HIV antibody test to document loss of maternal HIV antibodies (BIII).
- Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV nucleic acid test (AII).
- Diagnostic testing in children with non-perinatal exposure only or children with perinatal exposure aged  $>24$  months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV nucleic acid test may be necessary to diagnose HIV infection (AII).

**Note:** The National Clinical Consultation Center provides consultations on issues related to the management of perinatal HIV infection (1-888-448-8765; 24 hours a day, 7 days a week).

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# Clinical and Laboratory Monitoring of Pediatric HIV Infection

(Last updated May 22, 2018; last reviewed May 22, 2018)

## 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 and, if a child is **not** started on antiretroviral therapy (ART) after diagnosis, this monitoring **should be repeated** at least every 3 to 4 months thereafter (**AIII**).
- Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment-naïve patients (**AII**). Genotypic resistance testing is preferred for this purpose (**AIII**).
- After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical adverse effects and to support treatment adherence within 1 to 2 weeks, with laboratory testing for toxicity and viral load response recommended at 2 to 4 weeks after treatment initiation (**AIII**).
- Children on ART should be monitored for therapy adherence, effectiveness, and toxicities routinely (every 3 to 4 months) (**AII\***).
- Additional CD4 cell count and plasma viral load monitoring should be performed for evaluation of children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value (**AIII**). CD4 cell count can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years (**AII**). **Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence and disease progression (AIII).**
- Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ART regimens (**BIII**).
- The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, as mutations may not be detected once the drug has been discontinued. A history of all previously used ARV agents and available resistance test results must be reviewed when making decisions regarding the choice of new agents (**AII**).
- Viral co-receptor (tropism) assays **are recommended** whenever a CCR5 antagonist is being considered **for treatment (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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## When to Initiate Therapy in Antiretroviral-Naive Children (Last updated May 22, 2018; last reviewed May 22, 2018)

### Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive Infants and Children with HIV

Panel's Recommendations		
Aged	Criteria	Recommendation
<12 Months <sup>a</sup>	Regardless of clinical symptoms, immune status, or viral load	Urgent <sup>b</sup> treatment ( <b>AI</b> except <b>AI</b> for children aged ≥6 weeks to <12 weeks)
1 to <6 Years	CDC Stage 3-defining opportunistic illnesses <sup>c</sup>	Urgent <sup>b</sup> treatment ( <b>AI*</b> )
	CDC Stage 3 immunodeficiency: <sup>d</sup> CD4 <500 cells/mm <sup>3</sup>	
	Moderate HIV-related symptoms <sup>c</sup>	Treat <sup>e</sup> ( <b>AI</b> )
	CD4 cell count <sup>c</sup> 500–999 cells/mm <sup>3</sup>	
Asymptomatic or mild symptoms <sup>c</sup> <b>and</b> CD4 cell count <sup>c</sup> ≥1000 cells/mm <sup>3</sup>	Treat <sup>e</sup> ( <b>AI*</b> )	
≥6 Years <sup>e</sup>	CDC Stage 3-defining opportunistic illnesses <sup>c</sup>	Urgent <sup>a</sup> treatment ( <b>AI*</b> )
	CDC Stage 3 immunodeficiency: <sup>d</sup> CD4 <200 cells/mm <sup>3</sup>	
	Moderate HIV-related symptoms <sup>c</sup>	Treat <sup>b</sup> ( <b>AI</b> )
	CD4 cell count <sup>d</sup> 200–499 cells/mm <sup>3</sup>	
Asymptomatic or mild symptoms <sup>c</sup> <b>and</b> CD4 cell count ≥500 cells/mm <sup>3</sup>	Treat <sup>a,f</sup> ( <b>AI*</b> )	
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> I = One or more randomized trials in children<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion</p> <p><sup>†</sup> Studies that include children or children and adolescents but not studies limited to post-pubertal adolescents</p>		

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

<sup>a</sup> Treatment of infants aged ≤2 weeks is complex and an area of active investigation. See Antiretroviral Management of Newborns with Perinatal HIV

<sup>b</sup> Within 1–2 weeks, including an expedited discussion on adherence.

<sup>c</sup> See [Table 6](#) for definitions.

<sup>d</sup> CD4 cell counts should be confirmed with a second test to meet the treatment criteria before initiation of ART.

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

<sup>f</sup> For initiation of ART for adolescents aged ≥13 years and SMR of 4 or 5, see the [Adult and Adolescent Guidelines](#).

**Key to Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; SMR = sexual maturity rating

## What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated May 22, 2018; last reviewed May 22, 2018)

### Panel's Recommendations

- The selection of an initial regimen should be individualized based on several factors, including characteristics of the proposed regimen, patient characteristics, drug efficacy, potential adverse effects, patient and family preferences, and results of viral resistance testing (AIII).
- For treatment-naive children, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends initiating antiretroviral therapy with three drugs, including either an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor, plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone (AI\*).
- Table 7 provides a list of Panel-recommended regimens that are designated as Preferred or Alternative; recommendations vary by age, weight, and sexual maturity rating.

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# Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last updated November 15, 2017; last reviewed November 15, 2017)

## Panel's Recommendations

- All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
- Newborn ARV regimens—at gestational-age-appropriate doses—should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.
- The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission **(AIII)**. The uses of ARV regimens in newborns include:
  - **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition
  - **Empiric HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later confirmed to have HIV but also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process or during breastfeeding and who do not acquire HIV
  - **HIV Therapy:** The administration of a three-drug combination ARV regimen at treatment dosages (antiretroviral therapy [ART]) to newborns with confirmed HIV infection (see [Diagnosis of HIV Infection](#)).
- For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week zidovudine ARV prophylaxis regimen can be used **(BII)**.
- Newborns at higher risk of HIV acquisition should receive a combination ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk), including those born to women with HIV who:
  - Have not received antepartum or intrapartum ARV drugs **(AI)**, or
  - Have received only intrapartum ARV drugs **(AI)**, or
  - Have received antepartum ARV drugs but have not achieved viral suppression near delivery **(AII)**, or
  - Have primary or acute HIV infection during pregnancy **(AII)**, or
  - Have primary or acute HIV infection during breastfeeding **(AII)**.
- Newborns of women with unknown HIV status who test positive on expedited testing performed during labor or shortly after birth should initiate an ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk) **(AII)**. If supplemental testing is negative, the ARV regimen can be discontinued **(AII)**.
- For newborns with confirmed HIV, ART should be initiated **(AI)**.
- In the United States, the use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data **(BIII)**.
- Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care **(AIII)**.

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## Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV (Last updated May 22, 2018; last reviewed May 22, 2018)

### Panel's Recommendations

- All adolescents should receive maximally suppressive antiretroviral therapy (ART); this is urgent for those who are sexually active, considering pregnancy, or pregnant (AII).
- ART selection should consider the adolescent's individual needs and preferences (AIII).
- Reproductive health issues, including pregnancy intentions, contraceptive methods, safer sex techniques to prevent transmission of HIV and other sexually transmitted infections, pre-exposure prophylaxis (PrEP) for partners, pregnancy planning, and preconception care should be discussed regularly (AI).
- Providers should be aware of potential interactions between ART 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).

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## Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV (Last updated May 22, 2018; last reviewed May 22, 2018)

### Panel's Recommendations

- Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) 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 ART 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\*).

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## Management of Medication Toxicity or Intolerance (Last updated May 22, 2018; last reviewed May 22, 2018)

### 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 should be advised of the drug-related toxicity (AIII).
- In general, dose reduction is not a recommended option for management of ARV toxicity (AII\*).

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# Management of Children Receiving Antiretroviral Therapy (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Panel's Recommendations

- Children who have sustained virologic suppression on their current antiretroviral (ARV) regimen should be regularly evaluated for opportunities to change to a new regimen that facilitates adherence, simplifies administration, increases ARV potency, and decreases the risk of drug-associated toxicity (**AII**).
- All past regimens and past episodes of ARV therapy failure, tolerability, and all prior drug resistance testing results should be considered in order to avoid choosing new ARV drugs for which archived drug resistance would limit antiviral activity (**AIII**).
- Children should be carefully monitored after a change in treatment. Viral load measurement is recommended 2 to 4 weeks after a change in a child's ARV regimen (**BIII**).

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## Recognizing and Managing Antiretroviral Treatment Failure (Last updated May 22, 2018; last reviewed May 22, 2018)

### Panel's Recommendations

- The causes of antiretroviral (ARV) 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 ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen (**AI\***).
- ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results (**AI\***).
- The new regimen should include at least two, but preferably three, fully active ARV medications, with assessment of anticipated ARV activity based on past treatment history and resistance test results (**AII\***).
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay (**AI\***).
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future ARV options (**AII**).
- Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist (**AI\***).

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## Considerations About Interruptions in Antiretroviral Therapy (Last updated May 22, 2018, last reviewed May 22, 2018)

### Panel's Recommendations

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

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