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 April 16, 2019; last reviewed April 16, 2019)*

### 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 women should be tested as early as possible during each pregnancy (see *Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations* and *Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens*) *(AII)*.
- Partners of pregnant women should be encouraged to undergo HIV testing when their status is unknown *(AIII)*.
- Repeat HIV testing in the third trimester is recommended for pregnant women with negative initial HIV antibody tests who are at increased risk of acquiring HIV, including those who are receiving care in facilities that have an HIV incidence of ≥1 case per 1,000 pregnant women per year, those who reside in jurisdictions with elevated HIV incidence, or those who reside in states that require third-trimester testing (see *Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings*) *(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 should be available within 1 hour *(AII)*. If results are positive, intrapartum antiretroviral (ARV) prophylaxis should be initiated immediately *(AI)*, and infants should receive an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission as soon as possible, pending results of supplemental HIV testing *(AII)*. See *Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV* 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 the results for the mother or infant are positive, an appropriate infant ARV drug regimen should be initiated immediately, and the mother 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 doses (see *Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV*) *(AII)*.
- Results of maternal HIV testing should be documented in the newborn’s medical record and communicated to the newborn’s primary care provider *(AII)*.
- 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 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

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Panel’s Recommendations

- Virologic assays (i.e., HIV RNA and HIV DNA nucleic acid tests [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged <18 months with perinatal and postnatal HIV exposure; HIV antibody tests should not be used (AII).
- HIV RNA or HIV DNA NATs are generally equally recommended (AII).
- An assay that detects HIV non-B subtype viruses or Group O infections (e.g., an HIV RNA NAT or a dual-target total DNA/RNA test) is recommended for use in infants and children who were born to mothers with known or suspected non-B subtype virus or Group O infections (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)
- For infants at higher risk of perinatal HIV transmission, additional virologic diagnostic testing is recommended at birth (AII) and at 2 to 4 weeks after cessation of antiretroviral prophylaxis (BII).
- 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 nonbreastfed 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 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 NAT (AII).
- Diagnostic testing in children with nonperinatal 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 NAT may be necessary to diagnose HIV (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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1 Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents
Panel’s Recommendations

- **Absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of HIV diagnosis 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).**

- **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).**

- **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).**

- **After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical adverse effects and should receive support for 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 to evaluate 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 months–12 months) in children and adolescents who are adherent to therapy, who have CD4 cell count values that are well above the threshold for opportunistic infection risk and sustained virologic suppression, and who have had 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*). The use of tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist (AI*).**

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When to Initiate Therapy in Antiretroviral-Naive Children  (Last updated April 16, 2019; last reviewed April 16, 2019)

<table>
<thead>
<tr>
<th>Panel's Recommendations</th>
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</thead>
</table>
| • Antiretroviral therapy (ART) should be initiated in all antiretroviral-naive infants and children with HIV infection (AI, AI* or AII; see Table A for details).
  | o Rapid ART initiation (within 1-2 weeks of diagnosis) including an expeditated discussion of adherence is recommended for all children <12 months and those with CDC Stage 3-defining conditions.
  | o In other situations, sufficient time to fully assess and address issues associated with adherence should be allowed prior to ART initiation.
• Every 3 to 4 months, health care providers should closely monitor the virologic, immunologic, and clinical status of any child with HIV who has not initiated ART (AIII).

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 Months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Regardless of clinical symptoms, immune status, or viral load</td>
<td>Rapid initiation&lt;sup&gt;b&lt;/sup&gt; of treatment (AI, but AI for children aged ≥6 weeks to &lt;12 weeks)</td>
</tr>
<tr>
<td>1 Year to &lt;6 Years</td>
<td>CDC Stage 3-defining conditions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Rapid initiation&lt;sup&gt;b&lt;/sup&gt; of treatment (AI*)</td>
</tr>
<tr>
<td></td>
<td>CDC Stage 3 immunodeficiency&lt;sup&gt;d&lt;/sup&gt; CD4 cell count &lt;500 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td></td>
<td>Moderate HIV-related symptoms&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI*)</td>
</tr>
<tr>
<td></td>
<td>CD4 cell count&lt;sup&gt;i&lt;/sup&gt; 500–999 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI*)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or mild symptoms&lt;sup&gt;j&lt;/sup&gt; and CD4 cell count&lt;sup&gt;i&lt;/sup&gt; ≥1,000 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI*)</td>
</tr>
<tr>
<td>≥6 Years&lt;sup&gt;k&lt;/sup&gt;</td>
<td>CDC Stage 3-defining conditions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Rapid initiation&lt;sup&gt;b&lt;/sup&gt; of treatment (AI*)</td>
</tr>
<tr>
<td></td>
<td>CDC Stage 3 immunodeficiency&lt;sup&gt;d&lt;/sup&gt; CD4 cell count &lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td></td>
<td>Moderate HIV-related symptoms&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI)</td>
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<tr>
<td></td>
<td>CD4 cell count&lt;sup&gt;i&lt;/sup&gt; 200–499 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or mild symptoms&lt;sup&gt;j&lt;/sup&gt; and CD4 cell count&lt;sup&gt;i&lt;/sup&gt; ≥500 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treat&lt;sup&gt;f&lt;/sup&gt; (AI*)</td>
</tr>
</tbody>
</table>

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<sup>1</sup> Studies that include children or children and adolescents but not studies limited to post-pubertal adolescents

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

<sup>b</sup> Within 1 week–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 initiating ART.

<sup>e</sup> Allow sufficient time to fully assess and address issues associated with adherence prior to initiating therapy.

<sup>f</sup> Patients and caregivers, together with their health care providers, may (on a case-by-case basis) decide to defer therapy due to clinical and/or psychosocial factors. Patients should be monitored closely in these cases.

<sup>g</sup> For adolescents aged ≥13 years with SMRs of 4 or 5, see the Adult and Adolescent Antiretroviral Guidelines.

**Note:** Potential barriers to adherence should be assessed and discussed with children who have HIV and their caregivers before initiation of therapy (AIII).

**Key to Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; SMR = sexual maturity rating
Panel’s Recommendations

• The selection of an initial regimen should be individualized based on several factors, including the characteristics of the proposed regimen, the patient’s characteristics, drug efficacy, potential adverse effects, patient and family preferences, and the 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: a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone plus an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor (AI*).

• Table 7 provides a list of Panel-recommended regimens that are designated as Preferred or Alternative; recommendations vary by a patient’s age, weight, and sexual maturity rating.

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Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last Updated December 14, 2018; last reviewed December 14, 2018)

<table>
<thead>
<tr>
<th>Panel’s Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV (A1).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of perinatal transmission of HIV (AIII). The uses of ARV regimens in newborns include:</td>
</tr>
<tr>
<td>• <strong>ARV Prophylaxis:</strong> The administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.</td>
</tr>
<tr>
<td>• <strong>Empiric HIV Therapy:</strong> The administration of a three-drug ARV regimen to newborns at highest risk of perinatal acquisition of HIV. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later documented 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.</td>
</tr>
<tr>
<td>• <strong>HIV Therapy:</strong> The administration of a three-drug ARV regimen at treatment dosages (antiretroviral therapy [ART]) to newborns with documented HIV infection (see Diagnosis of HIV Infection).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• Newborns at higher risk of perinatal acquisition of HIV should receive a multi-drug ARV prophylaxis regimen or empiric HIV therapy based on clinician assessment of risk (see Tables 11 and 12 for recommended regimens). <strong>Newborns at higher risk of HIV acquisition</strong> include those born to women with HIV who:</td>
</tr>
<tr>
<td>• Have not received antepartum or intrapartum ARV drugs (A1), or</td>
</tr>
<tr>
<td>• Have received only intrapartum ARV drugs (A1), or</td>
</tr>
<tr>
<td>• Have received antepartum ARV drugs but without viral suppression near delivery (AII), or</td>
</tr>
<tr>
<td>• Have primary or acute HIV infection during pregnancy (AII), or</td>
</tr>
<tr>
<td>• Have primary or acute HIV infection during breastfeeding (AII).</td>
</tr>
<tr>
<td>• Newborns of women with unknown HIV status who test HIV 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).</td>
</tr>
<tr>
<td>• For newborns with HIV infection, ART should be initiated (A1).</td>
</tr>
<tr>
<td>• The use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (&lt;37 weeks gestational age) because of lack of dosing and safety data (BIII).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
</tbody>
</table>

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Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV  
(Last updated April 16, 2019; last reviewed April 16, 2019)

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 regimen selection should include consideration of 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 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).
- All adolescents living with HIV should be screened for mental health disorders and substance use disorders (AII).

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Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV  
(Last updated April 16, 2019; last reviewed April 16, 2019)

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).
- In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used (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 April 16, 2019; last reviewed April 16, 2019)

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, 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 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

In the United States, the majority of children living with HIV are receiving antiretroviral therapy (ART), making treatment-experienced children the norm. Providers may consider antiretroviral (ARV) regimen changes for the following reasons:

- **Treatment Simplification**: Modifying ARV regimens in children who are currently receiving effective ART in order to simplify the regimen.
- **Treatment Optimization**: Increasing the treatment potency or barrier to resistance of an effective, but older or potentially fragile, regimen or improving the adverse event profile.
- **Toxicity Management**: Recognizing and managing ARV drug toxicity or intolerance (see Management of Medication Toxicity or Intolerance).
- **Treatment Failure**: Recognizing and managing treatment failure (see Recognizing and Managing Antiretroviral Treatment Failure).

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 or barrier to resistance, and decreases the risk of drug-associated toxicity (AII).
- Before making changes to a patient's regimen, clinicians must carefully consider the patient's previous regimens, past episodes of ARV therapy failure, prior drug resistance test results, and the patient's ability to tolerate the new drug regimen (AIII).
- Archived drug resistance can limit the antiviral activity of a new drug regimen.
- Children should be carefully monitored after a change in treatment. Viral load measurement is recommended 2 weeks to 4 weeks after a change in a child's ARV regimen (BIII).

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Recognizing and Managing Antiretroviral Treatment Failure

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 treatment history and past 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 the development of additional drug resistance that could further limit future ARV drug options (AII).
- Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist (AI*).

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

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

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

Considerations About Interruptions in Antiretroviral Therapy

Panel's Recommendations

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

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

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

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