HIV in Infants and Children

Introduction

History of HIV in Children in United States

The first reports of HIV in children in the United States emerged in December 1982, when the Centers for Disease Control described four children under the age of 2 years who had unexplained immunodeficiency and opportunistic infections. Several subsequent published reports described young children with AIDS. In 1985, a highly publicized story emerged of a 13-year-old boy with hemophilia and AIDS who was banned from his middle school in Indiana because he had AIDS; this boy, Ryan White, captured the nation's attention as he courageously battled to maintain the right to attend school. On August 18, 1990, the historic Ryan White Comprehensive AIDS Resources Emergency (CARE) Act was passed by the United States Congress, named in honor of Ryan White, who had died 4 months earlier at age 18. In 1994, the Pediatric AIDS Clinical Trials Group (PACTG) 076 trial reported a three-part zidovudine regimen reduced perinatal HIV transmission by 67.5% when compared with placebo. In the United States, due to the widespread implementation of highly effective measures to prevent perinatal HIV transmission, the number of children born with HIV has dramatically declined, from a peak of more than 1,700 babies born with HIV per year in the early 1990s to fewer than 50 per year in recent years.

Unique Aspects of Pediatric HIV

Clinicians who provide care for infants and children with HIV should have awareness of the unique characteristics of these populations, integrate age-specific primary care measures with HIV management, and be sensitive to the social and developmental aspects involved in the care of young people living with HIV. Children living with HIV face unique challenges that necessitate special clinical care considerations. Although most principles and concepts related to the diagnosis and management of HIV are similar in adults and children, the following summarize some key aspects of pediatric HIV care:

- Making a diagnosis of HIV in a newborn is confounded by the transfer of maternal anti-HIV antibodies to the baby
- Interpretation of CD4 cell count values in children requires adjustment based on age-specific criteria
- Urgent initiation of antiretroviral therapy is indicated for infants and young children with HIV as they are at risk for rapid disease progression and death
- Antiretroviral medications have age-specific approvals with different dosing requirements
- Children present special challenges in terms of adherence to antiretroviral therapy

This Core Concept will focus on diagnosis and management of HIV in infants and children through age 12 years. The topics of Preventing Perinatal HIV Transmission and HIV in Adolescents and Young Adults are
addressed in separate Topic Reviews.
Epidemiology of HIV in Children Younger than Age 13

Almost all children younger than 13 years of age with HIV in the United States have acquired HIV via perinatal transmission.\[12,13\] The following summarizes key epidemiologic features of children younger than 13 years of age in the United States.

- At year-end 2021 in the United States, 1,262 children younger than age 13 were living with diagnosed HIV, which was approximately 0.1% of all persons living with diagnosed HIV (Figure 2).\[12\]
- In recent years, the number of children younger than age 13 living with diagnosed HIV in the United States has declined steadily (Figure 3).\[12\]
- Black children are disproportionately affected—at year end 2021 among children younger than age 13 years living with diagnosed HIV, 58% (731 of 1,262) were Black children (Figure 4).\[12\]
Staging of Pediatric HIV Disease

Staging

The initial evaluation of a child is an important time to determine the stage, or status, of the child’s HIV disease. In the 2014 case definition, stage 0 indicates early HIV, inferred from a negative or indeterminate HIV test result within 6 months prior to a confirmed positive result.[14] Stages 1, 2, and 3 are determined based on the CD4 count, stratified by age (Table 1).[14] The presence of an AIDS-defining (stage 3) opportunistic infection confers a stage 3 diagnosis regardless of the CD4 cell count or percentage. Stage unknown refers to a person with laboratory confirmation of HIV, but no information about CD4 cell count or percentage (and no information about the presence of AIDS-defining clinical conditions). The absolute CD4 count takes precedence over the CD4 percentage, even in children, and the percentage is only considered if the corresponding CD4 count is unknown; this change was made because clinical evidence suggests the CD4 percentage has little effect on the prognosis and may actually overestimate the clinical stage.[14]

Real Time Staging

In previous case definitions, a patient’s stage of HIV was based on the most advanced stage ever experienced, or the “life-time stage”. Once a patient progresses to a more advanced stage, their stage does not revert (or be upgraded) to any earlier stage. The updated 2014 staging system is more flexible, allowing for a patient’s status to change in either direction after diagnosis; this is helpful in describing a patient’s “real-time stage”, or the status of HIV disease in the present moment. Admittedly, this new staging system is somewhat vague and it remains unclear how clinicians will utilize this more flexible component of staging for surveillance purposes.[14]

Clinical Criteria for HIV Diagnosis

According to the 2014 case definition, clinical criteria for a confirmed case of HIV are met when there is a note in a medical record by a physician or other qualified medical provider that states that the patient has HIV, followed by either laboratory criteria meeting the case definition, presumptive evidence of HIV infection (e.g. receipt of HIV antiretroviral therapy or prophylaxis for an opportunistic infection), an otherwise unexplained low CD4 count, or an otherwise unexplained diagnosis of an opportunistic illness.[14]

AIDS-defining Clinical Conditions

In children with laboratory-confirmed HIV, stage 3 (AIDS) is defined based on laboratory criteria (CD4 cell count) or clinical conditions. The list of AIDS-defining clinical conditions is extensive.[14, 15] Note that lymphoid interstitial pneumonia (pulmonary lymphoid hyperplasia) has been removed from the list of AIDS-defining clinical conditions in children because this condition is associated with moderate rather than severe immunodeficiency.[14]
Diagnosis of HIV in Infants and Children

Recommended Diagnostic Tests

The greatest diagnostic challenges in young children occur with infants born to mothers with HIV. The diagnosis of HIV should be made as soon as possible in an infant exposed to HIV.[16] Note that, due to concerns for contamination with maternal blood, blood samples from the umbilical cord should not be used for diagnostic evaluation for HIV at birth. The following summarizes the tests to be utilized in the diagnosis of HIV in infants.[16]

- **Virologic Assays**: The diagnosis of HIV among infants and children younger than 18 months who are born to mothers with HIV is best made with the use of virologic assays (HIV nucleic acid testing [NAT]) that directly detect HIV RNA or HIV DNA.[16] The HIV RNA assays detect extracellular HIV RNA in plasma and the HIV DNA assays detect intracellular HIV DNA in peripheral blood mononuclear cells. Since false positive tests can occur with both HIV DNA and RNA assays, repeat HIV NAT should be done if possible in order to verify the initial positive test.[16]

- **HIV Antigen-Antibody Tests and p24 Antigen Tests**: The use of HIV-1/2 antigen-antibody immunoassays or the HIV p24 antigen test alone is not recommended in the setting of perinatal HIV exposure because of the lower sensitivity and specificity in the first months of life when compared with virologic tests, such as HIV nucleic acid testing.[16,17] Serologic HIV-1/2 antigen-antibody immunoassay testing can be used for HIV diagnosis in infants and children with non-perinatal HIV exposure or for perinatally-exposed children older than 24 months of age.

Determining HIV Risk Status of Infants Born to Mothers with HIV

For infants born to mothers with HIV, the recommended HIV diagnostic evaluation varies based on the estimated perinatal HIV transmission risk. The Pediatric ART Guidelines identify two levels of HIV acquisition risk for infants: low risk and high risk.[16]

- **Low Risk**: Infants born to mothers who—
  - Received antiretroviral therapy during pregnancy
  - Had sustained suppression of HIV RNA levels (usually defined as less than 50 copies/mL), *and*
  - Were adherent to their antiretroviral regimen

- **High Risk**: Infants born to mothers who—
  - Did not receive prenatal care;
  - Received no antepartum antiretroviral therapy or only intrapartum antiretroviral therapy;
  - Initiated antiretroviral therapy late in pregnancy (during the late second or third trimester);
  - Received a diagnosis of acute HIV infection during pregnancy or in labor; and/or
  - Had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received antiretroviral therapy but did not achieve sustained viral suppression

HIV Testing Schedule of Infants Born to Mothers with HIV

The following summarizes Pediatric ART Guidelines HIV testing recommendations for infants based on whether the infant is considered to be low-risk or high-risk for acquiring HIV (Figure 5).[16]

- **Recommended Testing Schedule for Infants at Low Risk**: For infants considered to be at low risk
of perinatal transmission, HIV NAT diagnostic testing should take place at three time points after birth: 14 to 21 days, 1 to 2 months, and 4 to 6 months.[16]

- **Recommended Testing Schedule for Infants at High Risk:** In general, HIV virologic testing (HIV NAT) for infants at high risk of perinatal HIV transmission should first be performed at birth, ideally prior to initiating an antiretroviral drug regimen. Regardless, presumptive HIV therapy should not be delayed. Additional virologic testing for infants considered to be at higher-risk of perinatal HIV transmission and those receiving combination antiretroviral prophylaxis should be done at 14 to 21 days, 1 to 2 months, 2 to 3 months and 4 to 6 months. Virologic testing (HIV NAT) is also indicated 2 to 6 weeks after cessation of antiretroviral prophylaxis (usually this is at 8 to 12 weeks of life).[16,18] The rationale for the extra testing 2 to 6 weeks after cessation of antiretroviral prophylaxis is that combination antiretroviral prophylaxis in infants exposed to HIV may diminish the sensitivity of diagnostic virologic assays normally performed at age 1 to 2 months.[16,18] If there are concerns that a newborn may be lost to follow-up for care, the infant should undergo virologic diagnostic testing at birth, even if they are at low risk for perinatal HIV transmission.[18]

### Testing for Infants with Perinatal Exposure who are Breastfed

For a parent with HIV who breastfeeds, virologic testing should be done for the infant at birth, 14 to 21 days, 1 to 2 months, and 4 to 6 months of age.[16] In the event that there is a gap of longer than 3 months occurs between the testing at 1 to 2 months and 4 to 6 months, then one additional virologic test should be performed.[16] After 6 months of age, virologic testing should be done every 3 months during ongoing breastfeeding. The Perinatal HIV Clinical Guidelines acknowledge limited data exist to inform the appropriate frequency of HIV RNA testing for the breastfeeding parent, but they suggest one strategy is to perform maternal HIV RNA testing every 1 to 2 months during breastfeeding.[19] At any point, if there is a detectable maternal HIV RNA level, expert consultation should be obtained and prompt testing of the infant with an HIV NAT should be performed.[19] If a person with a detectable HIV viral load continues to breastfeed, some experts recommend infant testing monthly for early detection of HIV in the setting of ongoing exposure.[19] Following cessation of breastfeeding, regardless of the child’s age, virologic tests should be performed 4 to 6 weeks, 3 months and 6 months post-cessation.[16,19]

### Confirmatory Testing

Any infant with a positive virologic assay should have a confirmatory test performed as soon as possible after the initial positive test result. In children 24 months of age or older, the diagnosis of HIV can also be confirmed with an HIV-1/2 antigen-antibody immunoassay testing.[16,18]

### Exclusion of HIV Diagnosis

The diagnosis of HIV can be excluded in a non-breastfed infant with:[16,18]

- Two negative virologic tests: one test at age 1 month or older (and at least 2 to 6 weeks after discontinuation of multi-drug antiretroviral prophylaxis) and a negative test at age 4 months or older,

or

- Two negative HIV antibody tests from separate specimens obtained at age 6 months or later

### HIV Testing for Infants and Children Born to Mothers with Unknown HIV Status

Newborn infants or children whose maternal HIV status is not known, such as those in foster care or adoptees, should be promptly tested for HIV using age-appropriate diagnostic testing.[20]

### Children Older than 24 Months or with Non-Perinatal HIV Exposure
For children with non-perinatal exposure to HIV or children with perinatal HIV exposure who are older than 24 months of age, the diagnostic testing approach should be the same as used to diagnose HIV in adolescents and young adults. This approach should utilize the approach outlined in the CDC/APHL HIV Laboratory Testing Guidelines.[13] The initial screening test consists of an HIV-1/2 antigen-antibody combination immunoassay and positive screening tests should be followed by testing with an HIV-1/2 antibody differentiation immunoassay.[13] A positive screening test followed by a negative differentiation test warrants further testing with an HIV RNA assay.[13] For more details on HIV diagnostic testing in adolescents and adults, see Lesson HIV Diagnostic Testing in Module 1.
Clinical and Laboratory Monitoring

Baseline Evaluation

At entry to care, children with HIV should have a complete medical history, physical examination, and laboratory evaluation.[21] This history should include a detailed social history component (including immunizations, nutrition, physical and social/emotional environment), evaluation for HIV-specific physical problems (e.g. growth delay, motor or cognitive neurological problems). Youth with perinatal acquisition of HIV appear to be particularly vulnerable to cognitive problems, especially in the executive function domain.[22,23,24] Baseline laboratory evaluation for all children diagnosed with HIV at entry into care should include the following:[21]

- HIV RNA level
- CD4 cell count
- HIV drug resistance genotype (if possible based on HIV RNA level)
- Complete blood count (with differential)
- Serum chemistries
- Lipid Panel
- Urinalysis
- Screening for hepatitis B virus (HBV), unless immunity to HBV is previously demonstrated
- HLA-B*5701 test (if abacavir is being considered as part of the initial antiretroviral therapy regimen)
- For children with HIV who relocate to the United States from other countries, clinicians should consider obtaining thyroid function tests, screening for tuberculosis infection, hepatitis serologic studies, lead levels, and screening for gastrointestinal parasites.

Routine Monitoring

In general, all children living with HIV should undergo regular evaluation for growth and development, clinical signs and symptoms. At each visit, the medical provider should address the efficacy, safety and tolerability of the antiretroviral regimen as well as assess adherence. These visits can be in-person or using telehealth communication platforms at the provider’s discretion and based on the comfort level of the child and guardian.[21]

- **Children Not Taking Antiretroviral Therapy**: For children who are not receiving antiretroviral therapy, absolute CD4 cell count and HIV RNA should be monitored every 3 to 4 months, regardless of whether they have HIV-related symptoms.[21]

- **Monitoring of Children after Initiating or Changing Antiretroviral Therapy**: After initiating or changing antiretroviral therapy, children should have an evaluation after 1 to 2 weeks and again after 2 to 4 weeks. Both of these evaluations should include a medical history, physical examination and evaluation for medication adherence, mental health assessment and care coordination of multidisciplinary services, such as nutrition counseling and case management.[21] The 2- to 4-week visit should include testing for an HIV RNA level and laboratory testing that varies depending on the antiretroviral regimen.[21]

- **Long-Term Monitoring of Children on Antiretroviral Therapy**: The long-term monitoring of children maintained on antiretroviral therapy should typically occur every 3 to 4 months and include the following: HIV RNA level, absolute CD4 cell count, chemistries, complete blood count with differential, medication toxicity and adherence assessment, and antiretroviral medication dosage adjustment for growth and weight if needed.[21] Urinalysis, lipid panel, and random plasma glucose should be obtained every 6 to 12 months.[21] Monitoring of CD4 cell count and laboratory studies to detect antiretroviral medication toxicity can be done less frequently (every 6 to 12 months) in children who have been clinically stable for at least 2 years and (1) are adherent on a stable antiretroviral therapy regimen, (2) have sustained virologic suppression, with HIV RNA levels less than 50 copies/mL, and (3) have a CD4 count above the threshold for opportunistic infection risk.[21]
contrast, HIV RNA monitoring should continue to be performed every 3-4 months in order to assess adherence to the antiretroviral regimen.[21]
- **Type of Immunologic Monitoring**: The use of absolute CD4 cell count is preferred for monitoring the immunologic status of children. For children younger than 5 years of age, monitoring CD4 percentage is an acceptable alternative.[21] The risk of disease progression associated with a specific CD4 count or percentage varies with the age of the patient, with younger children (less than 1 year of age) experiencing higher risk of progression and death.[25,26]
- **Children with Suspected Virologic, Immunologic, and/or Clinical Deterioration**: Evaluation of children with suspected virologic, immunologic, and/or clinical deterioration should ideally include expert consultation and, in the setting of virologic failure undergo adherence assessment and HIV drug resistance testing.[21]

**Interpreting Immunologic and Virologic Parameters in Children**

When interpreting immunologic laboratory parameters in children with HIV, age is a crucial determinant because of widely variable age-appropriate norms for absolute CD4 count and CD4 percentage. Young children typically have CD4 counts that are much higher than those seen in adults. For example, among children younger than 12 months of age who do not have any immunologic deficiency, most will have a CD4 count of at least 1,500 cells/mm$^3$. The normal CD4 count declines during the first few years of life. Conceptually, it is very important to understand that children with HIV, especially very young children, can develop HIV-related opportunistic infections at significantly higher CD4 cell counts than adults who develop HIV-related opportunistic infections.[27] In addition, HIV RNA values are also typically higher in very young children who acquire HIV perinatally than in adolescents and adults. Although high HIV RNA levels correlate with more rapid disease progression in adults, the predictive value for HIV RNA concentration in a specific child is only moderate; the range of HIV RNA values overlaps in young children who experience rapid disease progression and those who do not.[21]
Antiretroviral Treatment for Children with HIV

Principles of Antiretroviral Therapy in Children

Antiretroviral therapy has been shown to significantly reduce morbidity, mortality, and hospitalizations among children with HIV in the United States.\[28,29,30,31\] A large clinical trial that randomized infants 6 to 12 weeks of age with HIV to receive early antiretroviral therapy versus deferred therapy (based on CD4-related criteria) found a 75% reduction in mortality when using the more aggressive policy of early treatment of infants.\[31\] Studies in children have demonstrated benefits to earlier initiation of antiretroviral therapy at higher CD4 counts, including improved immune response, reduction in proviral reservoirs, and more rapid growth reconstitution.\[31,32,33,34,35\] Similar to adults, ongoing viral replication in children is believed to cause a persistent inflammatory state that increases the risk of developing non-AIDS complications, such as renal disease, cancer, liver disease, and cardiovascular disease.\[36,37\] Several studies have shown that initiating antiretroviral therapy is associated with decreased systemic inflammation, lower risk of cardiomyopathy, and improved neurocognitive outcomes.\[38,39,40\]

Recommendations for When to Start Antiretroviral Therapy

Given data regarding the association of antiretroviral treatment initiation with benefits for immunity, growth and neurodevelopmental outcomes in children, the Pediatric ART Guidelines now recommends rapid initiation of combination antiretroviral treatment for all children diagnosed with HIV infection, regardless of age, CD4 count, or HIV RNA level.\[41\] In some instances three-drug presumptive antiretroviral therapy is initiated for newborns who are at the highest risk of HIV acquisition, even prior to a confirmed diagnosis of HIV.\[42\] For infants younger than 12 months of age who are diagnosed with HIV, urgent initiation of antiretroviral therapy is critical since they have the greatest risk of accelerated HIV disease progression, clinical illness, and death.\[41\] For older asymptomatic children with diagnosed HIV, the data regarding the risks and benefits of immediate antiretroviral therapy are more limited. Since antiretroviral therapy initiated at a young age will be lifelong, simultaneously addressing barriers to adherence and assessing social support are particularly important to prevent development of antiretroviral drug resistance that would limit future options. Accordingly, regular and frequent follow-up with the child and caregiver(s) may be necessary during the period immediately following the start of antiretroviral therapy.\[41\]

Recommended Antiretroviral Regimens for Initial Therapy

The recommended antiretroviral therapy regimens in the Pediatric ART Guidelines are based on child’s age, including gestational age and weight.\[43\] The following table summarized the preferred recommendations based on age and weight, including preferred initial regimens and preferred dual nucleoside reverse

<table>
<thead>
<tr>
<th>Preferred Initial Regimens Based on Age and Weight at Time of Treatment Initiation</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Weight Restrictions</td>
</tr>
<tr>
<td>Newborns, Birth to Age &lt;14 Days[^{a,b}]</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>≥2 kg</td>
</tr>
<tr>
<td>Neonates ≥14 Days to Age &lt;4 Weeks</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>≥2 kg</td>
</tr>
<tr>
<td>Infants and Children Aged ≥4 Weeks</td>
<td>≥3 kg</td>
</tr>
</tbody>
</table>
### Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs

<table>
<thead>
<tr>
<th>Age</th>
<th>Dual-NRTI Backbone Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates Birth to Age 1 Month</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)(^g)</td>
</tr>
<tr>
<td></td>
<td>Zidovudine plus (Lamivudine or Emtricitabine)(^h)</td>
</tr>
<tr>
<td>Infants and Children Aged &gt;1 Month to &lt;2 Years</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)(^g)</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥2 Years with SMRs of 1–3</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)(^g)</td>
</tr>
<tr>
<td></td>
<td>Tenofovir alafenamide-emtricitabine(^i) in children and adolescents weighing ≥14 kg and receiving a regimen that contains an INSTI or an NNRTI; tenofovir alafenamide-emtricitabine(^i) in children and adolescents weighing ≥35 kg and receiving a regimen that contains a boosted PI</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years with SMRs of 4 or 5</td>
<td>Refer to Adult and Adolescent Antiretroviral Therapy Guidelines</td>
</tr>
</tbody>
</table>

Abbreviations: NRTIs – nucleoside reverse transcriptase inhibitors; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SMRs = sexual maturity rating

\(^a\) If treatment is scheduled to begin before a patient is aged 14 days, nevirapine or raltegravir are Preferred agents because they are the only options with dosing information available for this age group. While many pediatric experts favor initiating ART as soon as possible after birth in order to limit the establishment of viral reservoirs, available clinical trial data do not suggest that initiating treatment within the first 14 days of life leads to better clinical outcomes than initiating treatment after 14 days of age. Clinicians should consult an expert in pediatric HIV infection before initiating treatment in infants aged <14 days. Additional considerations regarding the use of nevirapine or raltegravir in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection. Switching from nevirapine to lopinavir-ritonavir should be considered when the infant is aged ≥14 days with a
postmenstrual age of 42 weeks (the span of time between the first day of the mother’s last menstrual period and birth, plus the time elapsed after birth); lopinavir-ritonavir has produced better clinical outcomes in studies of children aged <3 years than nevirapine. Data are limited on the clinical outcomes of using raltegravir in infants and children aged <2 years.

In general, lopinavir-ritonavir should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and postnatal age ≥14 days. (see the lopinavir-ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information).

Raltegravir granules can be administered to infants and children weighing ≥2 kg from birth to age 2 years. Oral RAL granules can be used up to a dose of 100 mg in the 14 to <20 kg weight band. Raltegravir pills or chewable tablets can be used in children aged ≥2 years. Chewable raltegravir tablets can be crushed and dispersed in liquid to infants as young as 4 weeks of age who weight at least 3 kgs.

Dolutegravir is recommended as a Preferred agent for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg. Dolutegravir dispersible tablets can be administered in infants and children aged ≥4 weeks and weighing ≥3 kg. Film-coated dolutegravir tablets can be used in children weighing ≥14 kg. A fixed-dose combination tablet that contains dolutegravir-abacavir-lamivudine is available in dispersible tablets for children weighing >10 kg to <25 kg and as a single tablet to be swallowed for children weighing ≥25 kg.

Bictegravir is available only as part of a fixed-dose combination tablet.
that contains bictegravir-tenofovir alafenamide-emtricitabine; this FDC tablet is recommended as a Preferred regimen for children weighing ≥14 kg. Two strengths of bictegravir-tenofovir alafenamide-emtricitabine are available, with dosing according to a child’s weight. The pediatric strength tablet of bictegravir (30 mg)-tenofovir alafenamide (15 mg)-emtricitabine (120 mg) is recommended if the child weighs ≥14 kg to <25 kg. The adult tablet bictegravir (50 mg)-tenofovir alafenamide (25 mg)-emtricitabine (200 mg) is recommended if the child weighs ≥25 kg.

Nevirapine should not be used in post-pubertal girls with CD4 counts >250/mm³, unless the benefit clearly outweighs the risk. Nevirapine is approved by the FDA for treatment of infants aged ≥15 days.

Abacavir is not approved by the FDA for use in neonates and infants aged <3 months. Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on safety of abacavir in infants when initiated at an age <3 months. An FDC tablet that contains abacavir-lamivudine is available for use in children weighing ≥25 kg. Abacavir has a risk for hypersensitivity reaction; perform HLA-B*5701 screening before initiating abacavir.

A fixed-dose tablet that contains zidovudine-lamivudine is available for use in children weighing ≥30 kg.

Tenofovir alafenamide plus emtricitabine is recommended as a Preferred combination for children and adolescents weighing ≥14 kg when used with an INSTI or NNRTI; an FDC tablet that contains tenofovir alafenamide-emtricitabine is available in two strengths, with dosage determined by a child’s weight.
Bictegravir-tenofovir alafenamide-emtricitabine is approved by the FDA for children weighing ≥14 kg as a single-tablet regimen (two strengths are available). Tenofovir alafenamide-emtricitabine is approved by the FDA for children weighing ≥25 kg when used in the single-tablet regimen elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine. Tenofovir alafenamide-emtricitabine plus a boosted PI is only recommended for use in children and adolescents weighing ≥35 kg.

Source:

- Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. What to start: regimens recommended for initial therapy of antiretroviral-naive children. April 11, 2023. [HIV.gov]

Antiretroviral Medication Information for Pediatric Use

For many of the approved antiretroviral agents, the FDA has stipulated specific age or weight restrictions based on limited available data in pediatric populations. Although starting regimens for children and adolescents typically consist of a select few of the best-studied regimens, a much more limited evidence base informs the assembly of salvage regimens. The Pediatric ART Guidelines maintain an excellent compendium of pediatric antiretroviral drug information that includes an overview of the FDA approval status of the antiretroviral medications in children, specific formulations, drug interactions, toxicities, and dosing recommendations in different aged children.[44] Although abacavir is presently not FDA-approved for use in infants younger than 3 months of age, it can be considered for use in newborns if zidovudine is not available or the infant has zidovudine-associated toxicity.[42] Dosing information for abacavir use in infants between birth and 3 months, based on pharmacokinetic simulation. None of the preferred 2-NRTI backbones in children up to 12 years of age include tenofovir DF due to concerns about bone toxicity, especially since children with perinatally-acquired HIV already have reduced bone mineral density.[43, 45, 46, 47] The Pediatric ART Guidelines are updated regularly as new data is available for dosing and the safety of antiretrovirals in infants and children and FDA approval status changes.[44]

Adherence with Antiretroviral Therapy

Poor adherence to antiretroviral therapy reduces the likelihood of virologic suppression, increases the risk of developing drug resistance mutations and virologic failure, limits future treatment options, and can lead to both disease progression and secondary transmission. Although the threshold for adherence associated with successful virologic suppression varies by individual drug as well as by individual patient characteristics, suboptimal adherence generally leads to poorer outcomes. Children with HIV often struggle with adherence due to complex dosing regimens, typical age-appropriate behaviors (toddlers, adolescents), dependency on an adult caregiver to reliably provide therapy, and social issues within the family unit, such as substance use or homelessness.[48] The Pediatric ART Guidelines recommend using antiretroviral regimens with reduced pill burden and once daily dosing frequency whenever feasible to improve adherence. Furthermore, it is recommended that providers monitor for adherence at every visit.[49] These strategies are organized in three categories: (1) initial intervention strategies, (2) medication strategies, and (3) follow-up intervention strategies.[49] To promote adherence, the Pediatric ART Guidelines recommend regular viral load monitoring
### Evidence-Based Approaches for Monitoring Medication Adherence

<table>
<thead>
<tr>
<th>Routine Assessment of Medication Adherence in Clinical Care</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor viral load.</td>
<td>Viral load monitoring should be done more frequently after initiating or changing medications.</td>
</tr>
<tr>
<td>Assess quantitative self-report of missed doses.</td>
<td>Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).</td>
</tr>
<tr>
<td>Elicit description of medication regimen.</td>
<td>Ask patient and/or caregiver about the name/appearance, number, frequency of medications.</td>
</tr>
<tr>
<td>Assess barriers to medication administration.</td>
<td>Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.</td>
</tr>
<tr>
<td>Monitor pharmacy refills.</td>
<td>Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.</td>
</tr>
<tr>
<td>Conduct announced and unannounced pill counts.</td>
<td>Approaches include asking patients to bring medications to clinic, home visits, or referral to community health nursing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeted Approaches to Monitor Adherence in Special Circumstances</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement directly observed therapy.</td>
<td>Include brief hospitalization if indicated.</td>
</tr>
<tr>
<td>Measure plasma drug</td>
<td>Can be considered for particular drugs.</td>
</tr>
</tbody>
</table>
concentration.

### Approaches to Monitor Medication Adherence in Research Settings

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure drug concentrations in hair.</td>
</tr>
<tr>
<td>Good measure of adherence over time.</td>
</tr>
<tr>
<td>Use electronic monitoring devices.</td>
</tr>
<tr>
<td>Medication Event Monitoring System [MEMS] caps, Wisepill</td>
</tr>
<tr>
<td>Use mobile phone-based technologies.</td>
</tr>
<tr>
<td>Interactive voice response, SMS text messaging</td>
</tr>
</tbody>
</table>

Source:
- Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Adherence to antiretroviral therapy in children and adolescents living with HIV. April 11, 2023. [HIV.gov]

### Management of Antiretroviral Toxicity

Children taking lifelong antiretroviral therapy need to be monitored for both acute and chronic adverse effects, which can potentially involve different organ systems.\(^{50,51,52}\) This is particularly important as new antiretroviral treatment options become available that do not have a long track record of pediatric use. The Pediatric ART Guidelines have compiled reference tables of potential adverse effects associated with different antiretroviral agents and these guidelines provide detailed summaries for the following types of adverse effects: central nervous system toxicity; dyslipidemia; gastrointestinal effects; hematologic effects; hepatic events; insulin resistance, asymptomatic hyperglycemia, and diabetes mellitus; lactic acidosis; lipodystrophy, lipohypertrophy, and lipatrophy; nephrotoxic effects; osteopenia and osteoporosis; and rash and hypersensitivity reactions.\(^{52}\) The implications of long-term exposure (from infancy or childhood) to antiretroviral medications remains an area of active study and it is unclear whether life expectancy will be altered in individuals who survive into adulthood with perinatally-acquired HIV.\(^{46}\)
Immunizations for Children Living with HIV

Immunization Guideline Resources

The Advisory Committee for Immunization Practices (ACIP) publishes annual guidelines for the use of vaccines for all children and adolescents, including specific recommendations for vaccines based on medical conditions.[53, 54, 55]

Immunization Recommendations for Children with HIV

All inactivated vaccines are safe to administer to children with HIV, irrespective of their immune status. Accordingly, all infants and children with HIV should receive inactivated vaccines per standard recommended pediatric schedules. Children with HIV may also need to receive additional vaccinations if the vaccines were not administered in infancy.[54, 55] For routine immunization recommendations for children with HIV, see the most recent recommendations in the ACIP Adult Immunization Schedule.[55]

Use of Live Vaccines in Children with HIV

The ACIP defines high-level immunosuppression for children aged 18 years or younger as a CD4 percentage less than 15 or an absolute CD4 count less than 200 cells/mm$^3$.[55]

- **Live Influenza Virus Vaccine**: The live attenuated influenza vaccine is not recommended for children and adolescents with HIV, regardless of CD4 cell count or percentage.[55]
- **Live Measles Mumps-Rubella (MMR) Vaccine**: This vaccine is recommended for children or adolescents with HIV, unless they have high-level immunosuppression (CD4 cell count less than 200 cells/mm$^3$ or CD4 percentage less than 15%).[55]
- **Live Rotavirus Vaccine**: Although rotavirus is a live vaccine, it is recommended (with precaution) for all children with HIV, according to the usual dosing schedule.[55]
- **Live Varicella Vaccine**: This vaccine is recommended for children or adolescents with HIV, unless they have high-level immunosuppression (CD4 cell count less than 200 cells/mm$^3$ or a CD4 percentage less than 15%).[55]
- **Dengue Vaccine**: Dengue vaccine should not be administered to children or adolescents with HIV if they have high-level immunosuppression (CD4 cell count less than 200 cells/mm$^3$ or a CD4 percentage less than 15%); dengue vaccine can be administered with precaution to children with HIV if they have a CD4 count of at least 200 cells/mm$^3$ and they have a CD4 percentage of at least 15%.[55]
Opportunistic Infections in Children

It is beyond the scope of this review to address the prevention and treatment of all opportunistic infections that occur in children with HIV. The Pediatric OI Guidelines provides detailed information regarding prevention and treatment of the major opportunistic infections that occur in children.[56] The following discussion will focus on the prevention of three important opportunistic infections that can occur in children: Pneumocystis Pneumonia, Toxoplasma encephalitis, and disseminated Mycobacterium avium complex.[57,58,59] For additional information on prevention of opportunistic infections in children and for information related to treatment of opportunistic infections in children, see the detailed discussion in the Pediatric OI Guidelines.[56]

**Pneumocystis Pneumonia Prophylaxis**

Prophylaxis against *Pneumocystis jirovecii* pneumonia is an extremely beneficial intervention among infants with HIV, especially for those infants not yet on antiretroviral therapy. The incidence of *Pneumocystis* pneumonia in children with HIV is highest during the first year of life, with cases peaking at 3 to 6 months of age.[58] In resource-limited settings, *Pneumocystis* pneumonia has been shown in autopsy studies to cause up to 44% of HIV-associated deaths in children with HIV.[60]

**Initiating Pneumocystis Pneumonia Prophylaxis in Children**

The Pediatric OI Guidelines recommend administering *Pneumocystis* pneumonia prophylaxis in children with HIV who meet the following age-specific requirements:[58]

- **Age younger than 12 months (including those who are HIV indeterminate):** All should receive *Pneumocystis* pneumonia prophylaxis, regardless of CD4 cell count or CD4 percentage.
- **Age 1 to 5 years:** CD4 count less than 500 cells/mm³ or CD4 percentage is less than 15%.
- **Age 6 to 12 years:** CD4 count less than 200 cells/mm³ or a CD4 percentage less than 15%

**Recommended Regimens for Pneumocystis Pneumonia Prophylaxis in Children**

Trimethoprim-sulfamethoxazole is the first choice for *Pneumocystis* pneumonia prophylaxis in infants and children.[58] This medication can be dosed daily or on three consecutive days per week. For those unable to take trimethoprim-sulfamethoxazole, acceptable alternatives include dapsone and atovaquone.[58] If the child is unable to tolerate any of these agents, aerosolized pentamidine can be used—if they are old enough to use nebulization with a Respirgard II nebulizer (typically older than 5 years of age).

**Discontinuing Pneumocystis Pneumonia Prophylaxis in Children**

All infants with confirmed HIV should continue *Pneumocystis* pneumonia prophylaxis until age 1 year and then undergo reassessment for the need for prophylaxis.[58] Infants who test HIV-indeterminate should continue *Pneumocystis* pneumonia prophylaxis until they are determined to not have HIV infection.[58] For children with HIV who are older than 1 year of age, discontinuing *Pneumocystis* pneumonia prophylaxis should be considered if the child has received combination antiretroviral therapy for at least 6 months and has surpassed the original age-specific CD4 count and percentage threshold for initiating prophylaxis and maintained above that threshold for at least 3 consecutive months.[58] For children who do not have virologic suppression, the CD4 count and percentage should be reassessed every 3 months and prophylaxis should be restarted if the age-specific threshold for prophylaxis is once again met.

**Prophylaxis Against Toxoplasma Encephalitis in Children**

*Toxoplasma gondii* is a protozoan parasite that can infect humans and cause encephalitis and more rarely, retinitis, pneumonitis, and disseminated disease. Risk factors for acquiring *T. gondii* include exposure to cats (particularly cat feces), eating undercooked red meat, or ingesting raw shellfish.[57]
Indications for Prophylaxis Against *Toxoplasma* in Children

The Pediatric OI Guidelines recommend administering *Toxoplasma* encephalitis prophylaxis in toxoplasma-seropositive children with HIV who meet the following age-specific thresholds:[57]

- **Age younger than 6 years:** CD4 percentage less than 15%
- **Age 6 years and older:** CD4 count less than 100 cells/mm³

Recommended Regimens for *Toxoplasma* Prophylaxis in Children

Trimethoprim-sulfamethoxazole is the preferred agent for *Toxoplasma* prophylaxis in all infants and children.[57] For those unable to take trimethoprim-sulfamethoxazole, the acceptable alternative is dapsone plus atovaquone.[57] Atovaquone with or without pyrimethamine can also be considered.

Discontinuing *Toxoplasma* Prophylaxis in Children

Discontinuing *Toxoplasma* prophylaxis should be considered if the child has received combination antiretroviral therapy for at least 6 months and has maintained a CD4 percentage above 15% for children younger than 6 years of age, and greater than 200 cells/mm³ for children 6 years of age and older for at least 3 consecutive months.[57] For children who do not have virologic suppression, the CD4 percentage should be reassessed every 3 months and prophylaxis should be restarted if the age-specific threshold for prophylaxis is once again met.[57]

Prophylaxis Against *Mycobacterium avium* complex (MAC) in Children

*Mycobacterium avium* is a ubiquitous organism that can cause disseminated disease in severely immunocompromised hosts. It is uncommon during the first year of life and its incidence increases with age and with declining CD4 count.

Indications for Prophylaxis Against MAC in Children

The Pediatric OI Guidelines recommend administering MAC prophylaxis to children with advanced immunosuppression, defined by age and CD4 count as:[59]

- **Children aged less than 1 year:** CD4 less than 750 cells/mm³
- **Children aged 1 year to less than 2 years:** CD4 less than 500 cells/mm³
- **Children aged 2 years to less than 6 years:** CD4 less than 75 cells/mm³
- **Children aged 6 years or older:** CD4 less than 50 cells/mm³

Recommended Regimens for MAC Prophylaxis in Children

The recommended regimen is azithromycin or clarithromycin (both available in suspensions).[59] Children who cannot take azithromycin or clarithromycin for prophylaxis may be offered rifabutin as an alternative, though clinicians should be aware of significant drug interactions associated with rifabutin, as well as a lack of pediatric data on its use.[59] Prior to initiating primary prophylaxis for MAC, a blood culture should be obtained to rule out preexisting disseminated disease.

Discontinuing MAC Prophylaxis in Children

For children older than 2 years of age with HIV, discontinuing MAC prophylaxis should be considered if the child has received combination antiretroviral therapy for at least 6 months and has surpassed the original age-specific CD4 count and percentage threshold for initiating prophylaxis (greater than 100 cells/mm³ for children at least 6 years of age and greater than 200 cells/mm³ for children aged 2 years to less than 6 years) and maintained above that threshold for at least 3 consecutive months.[59] The Pediatric OI Guidelines do not
make any specific recommendations for discontinuing prophylaxis in children younger than 2 years of age.
Summary Points

- In the United States, at year-end 2021, there was an estimated 1,262 children younger than age 13 were living with diagnosed HIV in the United States; this number represents approximately 0.1 percent of all persons living with HIV in the United States.
- The 2014 CDC Revised Case Surveillance Definition for HIV specifies criteria for staging HIV in children by age and CD4 cell count, which is closely aligned with adult staging and differs from the prior pediatric classification system that was based on separate immunologic and clinical categories.
- A virologic assay (HIV nucleic acid testing, or NAT) that directly detects HIV RNA or HIV DNA is required to diagnose HIV among perinatally-exposed infants younger than 18 months of age.
- For infants born to mothers with HIV with a low risk of transmission, the recommended HIV diagnostic evaluation includes HIV nucleic acid testing at three time points after birth: 14 to 21 days, 1 to 2 months, and 4 to 6 months. For higher risk infants, testing is also recommended at birth and 2 to 6 weeks after cessation of antiretroviral prophylaxis.
- The diagnosis of HIV can be excluded in a non-breastfed infant with (1) two negative virologic tests (at 1 month or later, and at 4 to 6 months or later), or (2) two or more negative antibody tests performed at 6 months of age or older.
- Monitoring for CD4 cell count and HIV RNA should be based on the child’s immune status, whether they are taking antiretroviral therapy, and whether they have suppressed HIV RNA levels.
- For women breastfeeding, most experts recommend maternal HIV RNA monitoring should be done every 1 to 2 months during breastfeeding. A detectable maternal HIV RNA level should prompt expert consultation.
- Antiretroviral therapy with rapid initiation is recommended for all infants and children, with special urgency for infants younger than 12 months of age.
- Preferred and alternative pediatric antiretroviral therapy regimens are based on a child’s age and special circumstances, and many antiretroviral agents have age restrictions based on limited data in pediatric populations.
- *Pneumocystis* pneumonia prophylaxis should be given to all children with HIV (or HIV indeterminate) who are less than 12 months of age, regardless of CD4 cell count or CD4 percentage. PCP prophylaxis in older children, as well as prophylaxis against *Toxoplasma* encephalitis *Mycobacterium avium* complex (MAC) disease in children of all ages, is based on degree of immunosuppression.
Citations

   [PubMed Abstract]

   [PubMed Abstract]

   [PubMed Abstract]

   [PubMed Abstract]

   [Ryan White]

   [History of Ryan White Care Act]

   [PubMed Abstract]

   [PubMed Abstract]

   [PubMed Abstract]

    [CDC]

    [CDC]

    [CDC]

13. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory
[PubMed Abstract]

Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Adherence to antiretroviral therapy in children and adolescents living with HIV. April 11, 2023.
Advisory Committee on Immunization Practices (ACIP).Catch-up immunization schedule for persons aged 4 months–18 years who start late or who are more than 1 month behind, United States, 2023.
Advisory Committee on Immunization Practices (ACIP). Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2023.
References


- Elizabeth Glaser Pediatric AIDS Foundation [EGPAF] -


  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

• Melvin AJ, Mohan KM. Response to immunization with measles, tetanus, and Haemophilus influenzae type b vaccines in children who have human immunodeficiency virus type 1 infection and are treated with highly active antiretroviral therapy. Pediatrics. 2003;111:e641-4. [PubMed Abstract]


Ross AC, O’Riordan MA, Storer N, Dogra V, McComsey GA. Heightened inflammation is linked to carotid intima-media thickness and endothelial activation in HIV-infected children. Atherosclerosis. 2010;211:492-8. [PubMed Abstract] -


Tassiopoulos K, Moscicki AB, Mellins C, et al. Sexual risk behavior among youth with perinatal HIV


Figures

Figure 1 Annual Number of Perinatally-Acquired HIV Infections, United States, 1978-2021

During the years 1978-1993, the estimates were generated through a back calculation method.

Source: Centers for Disease Control and Prevention.
Figure 2 Persons Living with Diagnosed HIV Infection in United States, by Age, Year End 2020

At year-end 2021, among the 1,072,267 persons living with diagnosed HIV, 1,262 (0.1%) were younger than 13 years of age.

Figure 3 Children Younger Than 13 Years of Age Living with Diagnosed HIV in United States, 2017-2021

Figure 4 Number of Children Younger Than 13 Years of Age Living with Diagnosed HIV, by Race/Ethnicity, United States, Year End 2021

Figure 5 Recommended Virologic Testing Schedules for Infants Exposed to HIV by Perinatal HIV Transmission Risk

Abbreviation: NAT = nucleic acid test (e.g., HIV RNA or HIV DNA PCR)


<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>14-21 days</th>
<th>1-2 months</th>
<th>2-3 months</th>
<th>4-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants at Low Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*NAT</td>
<td>NAT</td>
<td>NAT</td>
<td>NAT</td>
<td>NAT</td>
<td></td>
</tr>
<tr>
<td>Infants at High Risk</td>
<td><em>NAT</em></td>
<td>NAT</td>
<td>NAT</td>
<td><em>NAT</em></td>
<td>NAT</td>
</tr>
</tbody>
</table>

*Low Risk refers to infants born to mothers with HIV who received standard antiretroviral therapy during pregnancy, had sustained suppression of HIV RNA levels, and were adherent to their antiretroviral regimen.

High Risk infants refers to infants born to mothers with HIV who did not receive prenatal care; received no antepartum antiretroviral therapy or only intrapartum antiretroviral therapy; initiated antiretroviral therapy late in pregnancy (during the late second or third trimester); received a diagnosis of acute HIV infection during pregnancy or in labor; and/or had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received antiretroviral therapy but did not achieve sustained viral suppression.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Age on Date of CD4 Test</th>
<th>1 to &lt; 6 Years</th>
<th>&gt;6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4 cells/µL</td>
<td>CD4%</td>
<td>CD4 cells/µL</td>
</tr>
<tr>
<td>1</td>
<td>≥1,500</td>
<td>≥34</td>
<td>≥1,000</td>
</tr>
<tr>
<td>2</td>
<td>750-1,499</td>
<td>26-33</td>
<td>500-999</td>
</tr>
<tr>
<td>3</td>
<td>&lt;750</td>
<td>&lt;26</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>

*The stage is based primarily on the CD4 cell count; the CD4 cell count takes precedence over the CD4 percentage, and the percentage is considered only if the count is missing. If a Stage 3-defining opportunistic illness has been diagnosed, then the stage is 3 regardless of CD4 test results.

Source:

### Preferred Initial Regimens Based on Age and Weight at Time of Treatment Initiation

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight Restrictions</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns, Birth to Age &lt;14 Days&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>None</td>
<td>2NRTIs plus Nevirapine</td>
</tr>
<tr>
<td></td>
<td>≥2 kg</td>
<td>2NRTIs plus Raltegravir&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neonates ≥14 Days to Age &lt;4 Weeks</td>
<td>None</td>
<td>2NRTIs plus Lopinavir-ritonavir&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>≥2 kg</td>
<td>2NRTIs plus Raltegravir&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infants and Children Aged ≥4 Weeks</td>
<td>≥3 kg</td>
<td>2NRTIs plus Dolutegravir&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥2 Years</td>
<td>≥14 kg</td>
<td>2NRTIs plus Bictegravir&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years with SMRs of 4 or 5&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Refer to the Adult and Adolescent Antiretroviral Therapy Guidelines</td>
<td></td>
</tr>
</tbody>
</table>

### Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs

<table>
<thead>
<tr>
<th>Age</th>
<th>Dual-NRTI Backbone Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates Birth to Age 1 Month</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zidovudine plus (Lamivudine or Emtricitabine)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infants and Children Aged &gt;1 Month to &lt;2 Years</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥2 Years with SMRs of 1-3</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Tenofovir alafenamide-emtricitabine&lt;sup&gt;i&lt;/sup&gt; in children and adolescents weighing ≥14 kg and receiving a regimen that contains an INSTI or an NNRTI; tenofovir alafenamide-emtricitabine&lt;sup&gt;i&lt;/sup&gt; in children and adolescents weighing ≥35 kg and receiving a regimen that contains a boosted PI</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years with SMRs of 4 or 5</td>
<td>Refer to Adult and Adolescent Antiretroviral Therapy Guidelines</td>
</tr>
</tbody>
</table>

**Abbreviations:** NRTIs = nucleoside reverse transcriptase inhibitors; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SMRs = sexual maturity rating

<sup>a</sup> If treatment is scheduled to begin before a patient is aged 14 days, nevirapine or raltegravir are Preferred agents because they are the only options with dosing information available for this age group. While many pediatric experts favor initiating ART as soon as possible after birth in order to limit the establishment of viral reservoirs, available clinical trial data do not suggest that initiating treatment...
within the first 14 days of life leads to better clinical outcomes than initiating treatment after 14 days of age. Clinicians should consult an expert in pediatric HIV infection before initiating treatment in infants aged <14 days. Additional considerations regarding the use of nevirapine or raltegravir in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection. Switching from nevirapine to lopinavir-ritonavir should be considered when the infant is aged ≥14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother’s last menstrual period and birth, plus the time elapsed after birth); lopinavir-ritonavir has produced better clinical outcomes in studies of children aged <3 years than nevirapine. Data are limited on the clinical outcomes of using raltegravir in infants and children aged <2 years.

In general, lopinavir-ritonavir should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and postnatal age ≥14 days. (see the lopinavir-ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information).

Raltegravir granules can be administered to infants and children weighing ≥2 kg from birth to age 2 years. Oral RAL granules can be used up to a dose of 100 mg in the 14 to <20 kg weight band. Raltegravir pills or chewable tablets can be used in children aged ≥2 years. Chewable raltegravir tablets can be crushed and dispersed in liquid to infants as young as 4 weeks of age who weight at least 3 kgs.

Dolutegravir is recommended as a Preferred agent for infants, children, and adolescents aged ≥4
weeks and weighing ≥3 kg. Dolutegravir dispersible tablets can be administered in infants and children aged ≥4 weeks and weighing ≥3 kg. Film-coated dolutegravir tablets can be used in children weighing ≥14 kg. A fixed-dose combination tablet that contains dolutegravir-abacavir-lamivudine is available in dispersible tablets for children weighing >10 kg to <25 kg and as a single tablet to be swallowed for children weighing ≥25 kg.

Bictegravir is available only as part of a fixed-dose combination tablet that contains bictegravir-tenofovir alafenamide-emtricitabine; this FDC tablet is recommended as a Preferred regimen for children weighing ≥14 kg. Two strengths of bictegravir-tenofovir alafenamide-emtricitabine are available, with dosing according to a child’s weight. The pediatric strength tablet of bictegravir (30 mg)-tenofovir alafenamide (15 mg)-emtricitabine (120 mg) is recommended if the child weighs ≥14 kg to <25 kg. The adult tablet bictegravir (50 mg)-tenofovir alafenamide (25 mg)-emtricitabine (200 mg) is recommended if the child weighs ≥25 kg.

Nevirapine should not be used in post-pubertal girls with CD4 counts >250/mm³, unless the benefit clearly outweighs the risk. Nevirapine is approved by the FDA for treatment of infants aged ≥15 days.

Abacavir is not approved by the FDA for use in neonates and infants aged <3 months. Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on safety of abacavir in infants when initiated at an age <3 months. An FDC tablet that contains abacavir-lamivudine is available for use in children weighing ≥25 kg. Abacavir has a risk for hypersensitivity reaction; perform
| HLA-B*5701 screening before initiating abacavir.

| A fixed-dose tablet that contains zidovudine-lamivudine is available for use in children weighing ≥30 kg.

| Tenofovir alafenamide plus emtricitabine is recommended as a Preferred combination for children and adolescents weighing ≥14 kg when used with an INSTI or NNRTI; an FDC tablet that contains tenofovir alafenamide-emtricitabine is available in two strengths, with dosage determined by a child’s weight. Bictegravir-tenofovir alafenamide-emtricitabine is approved by the FDA for children weighing ≥14 kg as a single-tablet regimen (two strengths are available). Tenofovir alafenamide-emtricitabine is approved by the FDA for children weighing ≥25 kg when used in the single-tablet regimen elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine. Tenofovir alafenamide-emtricitabine plus a boosted PI is only recommended for use in children and adolescents weighing ≥35 kg.

Source:

- Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. What to start: regimens recommended for initial therapy of antiretroviral-naive children. April 11, 2023. [HIV.gov]
Table 3. **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

### Evidence-Based Approaches for Monitoring Medication Adherence

<table>
<thead>
<tr>
<th>Routine Assessment of Medication Adherence in Clinical Care</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor viral load.</td>
<td>Viral load monitoring should be done more frequently after initiating or changing medications</td>
</tr>
<tr>
<td>Assess quantitative self-report of missed doses.</td>
<td>Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).</td>
</tr>
<tr>
<td>Elicit description of medication regimen.</td>
<td>Ask patient and/or caregiver about the name/appearance, number, frequency of medications.</td>
</tr>
<tr>
<td>Assess barriers to medication administration.</td>
<td>Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.</td>
</tr>
<tr>
<td>Monitor pharmacy refills.</td>
<td>Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.</td>
</tr>
<tr>
<td>Conduct announced and unannounced pill counts.</td>
<td>Approaches include asking patients to bring medications to clinic, home visits, or referral to community health nursing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeted Approaches to Monitor Adherence in Special Circumstances</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement directly observed therapy.</td>
<td>Include brief hospitalization if indicated.</td>
</tr>
<tr>
<td>Measure plasma drug concentration.</td>
<td>Can be considered for particular drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approaches to Monitor Medication Adherence in Research Settings</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure drug concentrations in hair.</td>
<td>Good measure of adherence over time.</td>
</tr>
<tr>
<td>Use electronic monitoring devices.</td>
<td>Medication Event Monitoring System (MEMS) caps, Wisepill</td>
</tr>
<tr>
<td>Use mobile phone-based technologies.</td>
<td>Interactive voice response, SMS text messaging</td>
</tr>
</tbody>
</table>

Source:
- Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Adherence to antiretroviral therapy in children and adolescents living with HIV. April 11, 2023. [HIV.gov]