HIV in Infants and Children

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Section 6: Key Populations
Topic 1: HIV in Infants and Children

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Introduction

History of HIV in Children in United States

The first reports of HIV infection 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.[1] Several subsequent published reports described young children with AIDS.[2,3,4] 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 engaged in a courageous battle to have the right to attend school.[5] In 1988 Elizabeth Glaser, a mother of five, founded the Pediatric AIDS Foundation to act as a powerful advocacy voice for the needs of children living with HIV; the name of this organization was changed to the Elizabeth Glaser Pediatric AIDS Foundation.[6] 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.[7] 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.[8] This trial led to the 1995 U.S. Public Health Services recommendation for use of zidovudine to prevent perinatal HIV transmission.[9] In the United States, due to the widespread implementation of highly effective prevention measures, the number of children born with HIV infection has dramatically declined, from a peak of more than 1700 babies born with HIV per year in the early 1990s to fewer than 150 in recent years (Figure 1).[10,11,12] Due to the increased availability of antiretroviral medications for children, the HIV-related death rate for children has also decreased significantly.[13]

Unique Aspects of Pediatric HIV Infection

Although most principles and concepts related to the diagnosis and management of HIV infection are similar in adults and children, some key differences exist, including (1) making a diagnosis of HIV in a newborn is confounded by the transfer of maternal anti-HIV antibodies to the baby, (2) interpretation of CD4 cell count values in children requires adjustment based on age-specific criteria, (3) urgent initiation of antiretroviral therapy is indicated for infants and young children infected with HIV as they are at risk for rapid disease progression and death, (4) antiretroviral medications have age-specific approvals with different dosing requirements, and (5) children present special challenges in terms of adherence to antiretroviral therapy. Clinicians who provide care for infants and children with HIV infection 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.

Resources
Children living with HIV face unique challenges that necessitate special clinical care considerations. This Core Concept will focus on diagnosis and management of infants and children through age 12 who are living with HIV. A separate Core Concept addresses management of HIV in Adolescents and Young Adults. The following are key resources from the United States Department of Health and Human Services related to pediatric HIV infection.

- Pediatric ARV Guidelines
- Pediatric Opportunistic Infection Guidelines
- Perinatal Guidelines
Epidemiology of HIV in Children Younger than Age 13

As a result of the dramatic decline in the rate of perinatal HIV transmission in the United States, the number of children younger than age 13 living with HIV infection is fewer than 1% of all persons living with diagnosed HIV (Figure 2).[13] At year-end 2015, an estimated 2,300 children younger than age 13 were living with diagnosed HIV infection in the United States and this number decreased steadily from 2011 to 2015 (Figure 3).[13] Almost all children younger than 13 years of age who are living with diagnosed HIV infection in the United States acquired HIV via perinatal transmission.[13] During 2010-2013, the five states with the most number of perinatally-acquired HIV infections were Florida (48), Texas (44), Georgia (42), Louisiana (26), and Pennsylvania (21).[12] Black/African American and Hispanic/Latino children are disproportionately affected—at year end 2015 among children younger than age 13 years living with diagnosed HIV infection, 1,482 (61%) were black/African American, 308 (13%) Hispanic/Latino, and 297 (13%) white (Figure 4).[13] Increasingly, foreign-born children are contributing to the number of children with HIV in the United States. Since 2011, the number of foreign-born children diagnosed yearly with HIV has exceeded United States-born children.[14] For those children living with HIV infection, the use of modern effective combination antiretroviral therapy has significantly decreased their morbidity and mortality. The benefit of antiretroviral therapy is shown by the very low number of stage 3 AIDS diagnosed in children (Figure 5) and the extremely low number of deaths in children with HIV younger than age 13 (only 11 deaths from 2011 through 2015).[13]
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 infection, inferred from a negative or indeterminate HIV test result within 6 months prior to a confirmed positive result.[15] Stages 1, 2, and 3 are determined based on the CD4 count, stratified by age (Table 1).[15] 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 infection, 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.[15]

Real Time Staging

In previous case definitions, a patient’s stage of HIV infection was based on the most advanced stage ever experienced, or the “life-time stage”. Once a patient progressed to a more advanced stage, a patient’s stage would 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.[15]

Clinical Criteria for HIV Diagnosis

According to the 2014 case definition, clinical criteria for a confirmed case of HIV is 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 infection, 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.[15]

AIDS-defining Clinical Conditions

In children with laboratory-confirmed HIV infection, stage 3 (AIDS) is defined based on laboratory criteria (CD4 cell count) or clinical conditions. The list of AIDS-defining clinical conditions is extensive.[15,16] 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.[15]
Diagnosis of HIV Infection in Infants and Children

Recommended Diagnostic Tests

The greatest diagnostic challenges in young children occur with infants born to mothers with HIV infection. The diagnosis of HIV infection should be made as soon as possible in an infant exposed to HIV. The following summarizes recommendations in the Pediatric ARV Guidelines.[17]

- **Virologic Assays**: The diagnosis of HIV infection among infants and children younger than 18 months is best made with the use of virologic assays (HIV nucleic acid testing [NAT]) that directly detect HIV RNA or HIV DNA.[17] The HIV RNA assays detect extracellular HIV RNA in plasma and the HIV DNA assays detect intracellular HIV DNA in peripheral blood mononuclear cells. The timing of the virologic assays depends on whether the infant is considered at low risk or higher risk of perinatal HIV transmission (Figure 6).[17]

- **Serology Tests**: Serologic HIV tests, including antigen-antibody combination immunoassays and rapid HIV antibody tests, are generally not useful in diagnosing infants less than 18 months of age due to the passive transfer of maternal anti-HIV antibodies that may persist in the infant up to 18 months of age born to women with HIV.[18] Some experts utilize antibody testing for young children (who were born to mothers with HIV) at age 12 to 18 months to confirm the absence of HIV infection in a young child with negative virologic tests. By age 12 months, most infants have lost maternal HIV antibodies and by 18 months nearly all have lost maternal HIV antibodies. Serologic testing can be used for diagnosis in infants and children with non-perinatal HIV exposure or for perinatally-exposed children older than 24 months of age.

- **p24 Antigen Tests**: The use of HIV p24 antigen testing 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.[19]

**HIV Testing Schedule for Infants Born to Mothers with HIV**

For infants born to mothers with HIV infection, the recommended HIV diagnostic evaluation varies based on the estimated perinatal HIV transmission risk. The Pediatric ARV Guidelines identify two levels of risk for HIV infection in infants: low risk and higher risk.[17]

**Low Risk**

For infants considered to be at low risk of perinatal transmission, virologic diagnostic testing should take place at three time points after birth: 14 to 21 days, 1 to 2 months, and 4 to 6 months.[17] The Pediatric ARV Guidelines refer to low risk of HIV acquisition in infants as those born to mothers with HIV who received standard antiretroviral therapy during pregnancy and achieved sustained suppression of HIV RNA levels without concerns regarding maternal adherence.[17]

**Higher Risk**

In addition to the timepoints above, for infants considered to be at higher-risk of perinatal HIV transmission and those receiving combination antiretroviral prophylaxis, virologic diagnostic testing should also be considered at birth and 2 to 4 weeks after cessation of antiretroviral prophylaxis (usually this is at 8 to 10 weeks of life).[17] The rationale for the extra testing 2 to 4 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. The Pediatric ARV Guidelines define higher risk as infants born to mothers living with HIV who met any of the following criteria:[17]

- Did not receive prenatal care
- Did not receive antepartum or intrapartum antiretroviral therapy
- Received intrapartum antiretroviral drugs only
- Initiated antiretroviral therapy late in pregnancy (late second or third trimester)
- Were diagnosed with acute HIV infection during pregnancy
- Had detectable HIV viral loads close to the time of delivery
- Received combination antiretroviral therapy drugs and did not have sustained viral suppression.

**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 18 months of age or older, the diagnosis of HIV can also be confirmed with HIV positive HIV antibody testing.[17]

**Exclusion of HIV Diagnosis**

The diagnosis of HIV infection can be excluded in a non-breastfed infant with (1) two negative virologic tests (one at 1 month or later and another at 4 to 6 months or later) or (2) two or more negative antibody tests performed at 6 months of age or older. Some experts also confirm the absence of HIV infection at 12 to 18 months of age by performing an antibody test to document loss of maternal HIV antibodies.[17] Rarely, an HIV-uninfected infant continues to have residual maternal HIV antibodies out to 18 to 24 months. To confirm that these infants are late seroreverters (positive to negative HIV serology) repeat virologic testing should be done.[17]

**Children Older than 24 Months or with Non-Perinatal HIV Exposure**

For children with a 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.[20] 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.[20] A positive screening test followed by a negative differentiation test warrants further testing with an HIV RNA assay.[20] For more details on HIV diagnostic testing in adolescent and adults see the HIV Diagnostic Testing topic review in Module 1.
Clinical and Laboratory Monitoring

Baseline Evaluation

At entry to care, children with HIV infection should have a complete medical history, physical examination, and laboratory evaluation. 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), and evaluation for HIV-associated laboratory abnormalities (e.g. thrombocytopenia, leukopenia, elevated hepatic aminotransferase levels, and dyslipidemia). Perinatally infected youth appear to be particularly vulnerable to cognitive problems, especially in the executive function domain. Laboratory confirmation of HIV should be obtained, as well as baseline CD4 cell count, HIV RNA level, and HIV genotype testing. Screening for potential abacavir hypersensitivity reaction with the HLA-B*5701 test should be performed if the patient is being considered for antiretroviral therapy using a regimen that contains abacavir. A negative test HLA-B*5701 test does not rule out the possibility of a hypersensitivity reaction but makes it extremely unlikely.

Routine Monitoring

In general, children living with HIV infection should undergo evaluation for growth and development, clinical signs and symptoms, CD4 cell count, and HIV RNA every 3 to 4 months, regardless of whether they have started on antiretroviral therapy. In addition, for children on antiretroviral therapy, medication toxicity and adherence assessment, as well as possible antiretroviral medication dosage adjustment for growth, should be done at every visit. Urinalysis should be obtained at least once yearly to assess for HIV-associated nephropathy and for antiretroviral-associated toxicity; lipid monitoring should be performed at antiretroviral therapy initiation and then every 6 to 12 months thereafter to monitor for antiretroviral-induced hyperlipidemia. Additional CD4 count and HIV RNA testing should be performed if there is any change in clinical status or concern for virologic or immunological deterioration. Furthermore, when antiretroviral therapy is initiated or changed, children should be evaluated for adherence and side effects after 1 to 2 weeks, and laboratory testing for toxicity and virologic response (HIV RNA) should be checked at 2 to 4 weeks. In children, virologic suppression may take longer to achieve than in adults, possibly due to higher HIV RNA levels and less mature immune systems. Monitoring of CD4 cell count and antiretroviral medication toxicity laboratory studies 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, and (3) have a CD4 count above the threshold for opportunistic infection risk.

Use of CD4 Cell Count for Monitoring Immunologic Status

Similar to adults, the CD4 count or percentage and HIV RNA in children are independent predictors of mortality risk. The Pediatric ARV Guidelines recommend monitoring the immune status of children with HIV infection of all ages using the absolute CD4 cell count, with CD4 percentage as an alternative. Although CD4 percentage has historically been preferred for the monitoring of children, studies have not shown any improvement in prognostic value compared to absolute CD4 count. 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.

Interpreting Immunologic and Virologic Parameters in Children

When interpreting immunologic laboratory parameters in children with HIV infection, 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 1500 cells/mm³. The normal CD4 count declines during the first few years of life. It is conceptually very important to understand that children with HIV infection, especially very young children, can develop HIV-related opportunistic infections at significantly higher CD4 cell counts than adults who develop HIV-related opportunistic infections.[32] In addition, HIV RNA values are also typically higher in very young children who acquired 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 of Pediatric HIV Infection

Principles of Antiretroviral Therapy in Children

Antiretroviral therapy significantly reduces morbidity, mortality, and hospitalizations among children living with HIV infection in the United States.[33,34,35,36] A large clinical trial that randomized infants 6 to 12 weeks of age with HIV infection 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.[36] 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.[36,37,38,39,40,41,42] 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.[43,44] Several studies have shown that initiating antiretroviral therapy is associated with decreased systemic inflammation, lower risk of cardiomyopathy, and improved neurocognitive outcomes.[45,46,47]

Recommendations for When to Start Antiretroviral Therapy

The Pediatric ARV Guidelines recommend antiretroviral treatment for all children. The urgency for when to start antiretroviral therapy varies based on the child's age and pretreatment CD4 cell count (Table 2).[48] Urgent therapy is recommended for infants younger than 12 months of age, regardless of clinical symptoms and CD4 count and for all older children with CDC Stage 3 clinical or immunologic disease.[48] For older asymptomatic children, 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, issues of adherence are particularly important to prevent development of antiretroviral drug resistance that would limit future options. Accordingly, in some situations, it may be beneficial to have additional time to spend addressing barriers to adherence and assessing social supports that will allow families to successfully implement antiretroviral therapy.[48] Unlike for adults, initiating antiretroviral therapy for the purpose of reducing secondary sexual transmission of HIV is not a compelling reason to start antiretroviral therapy in children younger than age 13.

Recommended Antiretroviral Regimens for Initial Therapy

Similar to recommendations for when to start antiretroviral therapy, the recommendations for preferred and alternative regimens are based on the child’s age or special circumstances.[49] For antiretroviral-naïve children, the Pediatric ARV Guidelines recommend using a three-drug regimen that includes a dual-nucleoside reverse transcriptase inhibitors (NRTI) backbone plus a third anchor drug that consists of a boosted protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (ISTI) (Table 3).[49] Among the first-line options, the selection of a particular regimen should take into account results of drug resistance testing, complexity of dosing (including food requirements), palatability, individual patient and/or family preference. There is considerable debate and ongoing research into the relative efficacy, durability, and toxicity (in particular, the impact on growth and metabolic parameters) of using PIs or NNRTIs as the anchor drug in a pediatric regimen.[50,51,52,53,54] The tolerability and cleaner profile of the integrase strand transfer inhibitors make this class particularly appealing in the treatment of pediatric HIV infection. Recommendations for specific preferred and alternate regimens change frequently as pharmacokinetic and safety data in infants and children become available for newer antiretroviral medications.

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 ARV 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 pediatric patients.[55] The Pediatric ARV Guidelines do not include tenofovir DF in any of the preferred 2-NRTI backbones in children up to 12 years of age due to concerns about bone toxicity, especially since children with perinatally-acquired HIV already have reduced bone mineral density.[49,56,57,58] The Pediatric ARV Guidelines are updated regularly as new data is available for dosing and safety of antiretrovirals in infants and children and FDA-approval status changes.[55]

Adherence to 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 infection 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.[59] The Pediatric ARV Guidelines emphasize the importance of monitoring for adherence and provide strategies that can be employed to improve adherence among young people with HIV infection.[60] These strategies are organized in three categories: (1) initial intervention strategies, (2) medication strategies, and (3) follow-up intervention strategies.[60]

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.[61,62,63] This is particularly important as new antiretroviral treatment options become available that do not have a long track record of pediatric use. The Pediatric ARV 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 lipoatrophy; nephrotoxic effects; osteopenia and osteoporosis; peripheral nervous system toxicity; and rash and hypersensitivity reactions.[63] 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 infection.[57]
Immunizations for Children Living with HIV

Immunization Guideline Resources

The publishes annual guidelines for the use of vaccines for all children and adolescents, including specific recommendations for vaccinbased on medical conditions.[64,65,66] The 2014 IDSA Vaccine Guidelines for the Immunocompromised Host also issued recommendations for vaccination of the immunocompromised adults and children.[67]

Immunization Recommendations for Children Living with HIV

All inactivated vaccines are safe to administer to children living with HIV, irrespective of their immune status. Accordingly, all infants and children living with HIV should receive inactivated vaccines per standard recommended pediatric schedules. Children with HIV infection may also qualify for additional vaccinations, including the pneumococcal polysaccharide vaccine (PPSV23) and Haemophilus influenzae type b (Hib) vaccine if these vaccines were not administered in infancy.[68] The meningococcal vaccine series should be initiated earlier in children with HIV, with the age of initiation and number of doses dependent on meningococcal vaccine type.[66] Measles-mumps-rubella (MMR) and varicella vaccines are recommended for children or adolescents with HIV with low-level or no immunosuppression, but should not be administered with high-level immunosuppression.[66] The ACIP defines high-level immunosuppression for children aged 18 years or younger as a CD4 percentage less than 15 or a total CD4 count less than 200 cells/mm$^3$).[66] The live attenuated influenza vaccine has been shown to be safe when administered to children without high-level immunosuppression, but it is generally not recommended for children and adolescents living with HIV.[66,67] Although rotavirus is a live vaccine, it is recommended (with precaution) for all children living with HIV, according to the usual dosing schedule.[66] Zoster vaccine live (ZVL) and the quadrivalent measles, mumps, and rubella-varicella (MMRV) vaccine are not recommended for use in children living with HIV at any age.
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 living with HIV. The Pediatric Opportunistic Infection Guidelines provide detailed information regarding prevention and treatment of the major opportunistic infections that occur in children. 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. For additional information on prevention of opportunistic infections in children and for information related to treatment of opportunistic infections in children, see the details discussion in the Pediatric Opportunistic Infection Guidelines.

Pneumocystis Pneumonia Prophylaxis

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

Initiating Pneumocystis Pneumonia Prophylaxis in Children

The Pediatric Opportunistic Infection Guidelines recommend administering PCP prophylaxis in children with HIV infection who meet the following age-specific requirements:

- **Age younger than 12 months (including those who are HIV indeterminate):** All should receive PCP 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. For those unable to take trimethoprim-sulfamethoxazole, acceptable alternatives include dapsone and atovaquone. 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 infection and those who test HIV-indeterminate should continue Pneumocystis pneumonia prophylaxis until age 1 year and then undergo reassessment for the need for prophylaxis. For children with HIV infection 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. The child's 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.[70]

**Indications for Prophylaxis Against Toxoplasma in Children**

The Pediatric Opportunistic Infection Guidelines recommend administering *Toxoplasma* encephalitis prophylaxis in toxoplasma-seropositive children with HIV infection who meet the following age-specific thresholds:[70]

- **Age younger than 6 years**: CD4 percentage less than 15%
- **Age 6 years and older**: CD4 count less than 100 cells/mm$^3$

**Recommended Regimens for Toxoplasma Prophylaxis in Children**

Trimethoprim-sulfamethoxazole is the preferred agent for *Toxoplasma* prophylaxis in all infants and children.[70] For those unable to take trimethoprim-sulfamethoxazole, the acceptable alternative is dapsone plus atovaquone.[70] 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/mm$^3$ for children 6 years of age and older for at least 3 consecutive months.[70] 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.[70]

**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 Opportunistic Infection Guidelines recommend administering MAC prophylaxis to children with advanced immunosuppression, defined by age and CD4 count as:[72]

- **Children aged less than 1 year**: CD4 less than 750 cells/mm$^3$
- **Children aged 1 to less than 2 years**: CD4 less than 500 cells/mm$^3$
- **Children aged 2 to less than 6 years**: CD4 less than 75 cells/mm$^3$
- **Children aged 6 years or older**: CD4 less than 50 cells/mm$^3$

**Recommended Regimens for MAC Prophylaxis in Children**

The recommended regimen is azithromycin or clarithromycin (both available in suspensions).[72] 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.[72] 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 infection, 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/mm$^3$ for children aged 6 years of age and older; and greater than 200 cells/mm$^3$ for children aged 2 to less than 6 years) and maintained above that threshold for at least 3 consecutive months.[72] The Pediatric Opportunistic Infection Guidelines do not make any specific recommendations for discontinuing prophylaxis in children younger than 2 years of age.
Summary Points

- The 2014 CDC Revised Case Surveillance Definition for HIV specifies criteria for staging HIV infection 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 infection among perinatally exposed infants younger than 18 months of age.
- For infants born to mothers with HIV infection, 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.
- The diagnosis of HIV infection 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.
- CD4 cell count and HIV RNA should be measured at diagnosis and then every 3 to 4 months regardless of whether the child is taking antiretroviral therapy; children taking antiretroviral therapy should also be assessed for adherence and toxicity every 3 to 4 months.
- The risk of disease progression associated with a specific CD4 count or percentage varies with the age of the patient, with younger children experiencing higher risk of progression and death.
- Antiretroviral therapy should be offered to all infants and children with HIV infection, regardless of clinical status, CD4 count, or CD4 percentage. Urgent antiretroviral therapy is recommended for infants younger than 12 months and for older children with CDC Stage 3 clinical or immunologic disease.
- 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 infection (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.
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- 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]


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Figures

Figure 1 Annual Number of Live-Born Infants with Perinatal HIV Infection, United States, 1978-2013

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

At year end 2015, among the 973,846 persons living with diagnosed HIV, 2,322 (0.24%) were younger than age 13.

Figure 3 Children Younger Than 13 Years of Age Living with Diagnosed HIV, 2011-2015

Figure 4 Number of Children Younger Than 13 Years of Age Living with Diagnosed HIV by Race/Ethnicity, United States, Year End 2015

Figure 5 Stage 3 AIDS Diagnosis Among Children Younger Than 13 Years of Age: 1992-2016, United States and 6 Dependent Areas

Figure 6 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) *For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 4 weeks after cessation of antiretroviral prophylaxis (i.e. at 8–10 weeks of life). "Low Risk" refers to infants born to mothers with HIV who received standard antiretroviral therapy during pregnancy and achieved sustained suppression of HIV RNA levels and there were no concerns regarding maternal adherence. "Higher risk" infants are those born to mothers with HIV who did not receive prenatal care, did not receive antepartum or intrapartum antiretroviral therapy, received only intrapartum antiretroviral medications, initiated antiretroviral therapy late in pregnancy (late second or third trimester), diagnosed with acute HIV infection during pregnancy, or had detectable HIV viral loads close to the time of delivery.

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;1 Year</th>
<th>1 to &lt; 6 Years</th>
<th>≥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:
Table 2. HHS Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>Regardless of clinical symptoms, immune status, or viral load</td>
<td>Urgent(^b) treatment (\textbf{All} except \textbf{Al} for (\geq 6) weeks to &lt;12 weeks of age)</td>
</tr>
<tr>
<td>1 to&lt; 6 Years</td>
<td>CDC State 3-defining opportunistic illnesses(^c)</td>
<td>Urgent(^b) treatment (\textbf{AI*})</td>
</tr>
<tr>
<td></td>
<td>CDC Stage 3 immunodeficiency(^d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;500 cells/mm(^3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate HIV-related symptoms(^e)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 cell count(^c) 500–999 cells/mm(^3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or mild symptoms(^c) and CD4 cell count(^c) (\geq 1000) cells/mm(^3)</td>
<td></td>
</tr>
<tr>
<td>(\geq 6) Years</td>
<td>CDC State 3-defining opportunistic illnesses(^c)</td>
<td>Urgent(^a) treatment (\textbf{AI*})</td>
</tr>
<tr>
<td></td>
<td>CDC Stage 3 immunodeficiency(^d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;200 cells/mm(^3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate HIV-related symptoms(^e)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 cell count(^d) 200–499 cells/mm(^3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or mild symptoms(^c) and CD4 cell count(^d) (\geq 500) cells/mm(^3)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

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

\(^a\) For infants ≤2 weeks, see Specific Issues in Antiretroviral Therapy for Neonate

\(^b\) Within 1–2 weeks, including an expedited discussion on adherence

\(^c\) See definitions in Table 6

\(^d\) CD4 cell counts should be confirmed with a second test to meet the treatment criteria before initiation of ART.

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

Source:

- Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. When to initiate therapy in antiretroviral-naive children. May 22, 2018. [AIDSinfo]
### Table 3. HHS Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

#### Antiretroviral Regimens Recommended for Initial Therapy in Children

**Preferred Regimens**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Preferred Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants, Birth to &lt;14 Days&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2NRTIs plus Nevirapine&lt;br&gt;2NRTIs plus Raltegravir</td>
</tr>
<tr>
<td>Children Aged ≥14 Days to &lt;3 Years</td>
<td>2NRTIs plus Lopinavir-ritonavir&lt;br&gt;2NRTIs plus Raltegravir&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2NRTIs plus Atazanavir plus Ritonavir&lt;br&gt;2NRTIs plus twice daily Darunavir&lt;sup&gt;d&lt;/sup&gt; plus Ritonavir</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2NRTIs plus Atazanavir plus Ritonavir&lt;br&gt;2NRTI plus Dolutegravir&lt;sup&gt;g&lt;/sup&gt; (only if weight ≥30 kg)</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 1-3</td>
<td>2NRTIs plus Atazanavir plus Ritonavir&lt;br&gt;2NRTI plus Dolutegravir&lt;sup&gt;g&lt;/sup&gt; (only if weight ≥30 kg) &lt;br&gt;2NRTIs plus once daily Darunavir plus Ritonavir (only if weight ≥40 kg) &lt;br&gt;Elvitegravir-Cobicistat-Tenofovir alafenamide-Emtricitabine (only if weight ≥35 kg)</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 4 or 5</td>
<td>Refer to Adult and Adolescent Antiretroviral Therapy Guidelines</td>
</tr>
</tbody>
</table>

**Alternative Regimens**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Preferred Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥14 Days to &lt;3 Years</td>
<td>2NRTIs plus Nevirapine&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children Aged ≥3 Months to &lt;3 Years and Weighing ≥10 kg</td>
<td>2NRTIs plus Atazanavir plus Ritonavir</td>
</tr>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2NRTIs plus Efavirenz&lt;sup&gt;h&lt;/sup&gt;&lt;br&gt;2NRTIs plus Lopinavir-ritonavir</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2NRTIs plus twice daily Darunavir plus Ritonavir&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;2NRTIs plus Efavirenz&lt;sup&gt;h&lt;/sup&gt;&lt;br&gt;Elvitegravir-Cobicistat-Tenofovir alafenamide-Emtricitabine (only if weight ≥35 kg)</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I-III)</td>
<td>2NRTIs plus Efavirenz&lt;sup&gt;h&lt;/sup&gt;&lt;br&gt;2NRTIs plus Raltegravir&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;2NRTIs plus Rilpivirine&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Preferred Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, Birth to Age &lt;3 Months</td>
<td>Zidovudine plus (Lamivudine or Emtricitabine)</td>
</tr>
<tr>
<td>Children Aged ≥3 Months and &lt;6 Years</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)&lt;br&gt;Zidovudine plus (Lamivudine or Emtricitabine)</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥6 Years and SMR 1-3</td>
<td>Abacavir plus (Lamivudine or Emtricitabine)&lt;br&gt;Tenofovir alafenamide-Emtricitabine</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 4 or 5</td>
<td>Refer to Adult and Adolescent Antiretroviral Therapy Guidelines</td>
</tr>
</tbody>
</table>
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs

<table>
<thead>
<tr>
<th>Children Age ≥3 Months</th>
<th>Zidovudine plus Abacavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Age ≥2 Years to 12 Years</td>
<td>Tenofovir DF plus (Lamivudine or Emtricitabine)</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥6 Years and SMR 1-3</td>
<td>Zidovudine plus (Lamivudine or Emtricitabine)</td>
</tr>
</tbody>
</table>

a. If treatment initiation is planned prior to 14 days of age, nevirapine is the Preferred agent. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Consultation with an expert in pediatric HIV infection should be sought. A change from nevirapine to lopinavir-ritonavir should be considered when the infant is aged ≥14 days and 42 weeks post-gestational age, based on infant genotype and the better outcomes of lopinavir-ritonavir in children aged <3 years.

b. 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.

c. Raltegravir pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children aged 4 weeks to 2 years.

d. Darunavir once-daily should not be used in children aged <12 years or weighing <40 kg or if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. Darunavir + ritonavir is an Alternative recommendation for children aged ≥6 years to <12 years because there are options that can be administered once-daily. It is preferred for adolescents aged ≥12 years and not sexually mature (SMR I–III) where once-daily administration is possible.

e. Dolutegravir is recommended only for children and adolescents weighing ≥30 kg.

f. Elvitegravir is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide are recommended as Preferred for children and adolescents weighing ≥35 kg. Tablets containing elvitegravir-cobicistat-emtricitabine-tenofovir DF are recommended only for children and adolescents weighing ≥35 kg, and in SMR IV or V.

g. Nevirapine should not be used in post-pubertal girls with a CD4 cell count >250/mm$^3$, unless the benefit clearly outweighs the risk. Nevirapine is FDA-approved for treatment of infants aged ≥15 days.

h. Efavirenz is licensed for use in children aged ≥3 months who weigh ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years.

i. Rilpivirine should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

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. May 22, 2018. [AIDSinfo]