HIV in Infants and Children

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Module 6: Key Populations
Lesson 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] 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.[6] 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.[7] This trial led to the 1995 U.S. Public Health Services recommendation for use of zidovudine to prevent perinatal HIV transmission.[8] In the United States, due to the widespread implementation of highly effective prevention measures, 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 75 per year in recent years (Figure 1).[9, 10, 11]

Unique Aspects of Pediatric HIV

Although most principles and concepts related to the diagnosis and management of HIV 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 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. 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 acquired HIV via perinatal transmission.[12] The following summarizes key epidemiologic features of children younger than 13 years of age in the United States.

- 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 with HIV is fewer than 0.2% of all persons with diagnosed HIV (Figure 2).[12]
- At year-end 2018, an estimated 1,912 children younger than age 13 were diagnosed with HIV in the United States and this number decreased steadily from 2014 to 2018 (Figure 3).[12]
- Black/African American children are disproportionately affected—at year end 2018 among children younger than age 13 years with diagnosed HIV, 60% (1,152 of 1,912) were black/African American (Figure 4).[12]
- 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.[13]
- For children with HIV, the benefit of routine use 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 10 deaths from 2014 through 2018).[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 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.[14]

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, 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 Infection 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. The following summarizes recommendations in the Pediatric ARV Guidelines.\[16\]

- **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. The timing of the virologic assays depends on whether the infant is considered at low risk or higher risk of perinatal HIV transmission based on the mother’s HIV RNA levels (Figure 6).\[16,17\]

- **Antibody Tests**: For infants born to mothers with HIV, use of HIV antibody tests has limited diagnostic utility up to 18 months of age due to the high HIV false-positive rates from passive transfer of maternal anti-HIV antibodies.\[18\] Some experts utilize antibody testing for young children (who were born to mothers with HIV) at age 12 to 18 months, since by age 12 months, most infants have lost maternal HIV antibodies, and by 18 months nearly all have lost maternal HIV antibodies. Serologic HIV antibody 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.

- **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.\[16,19\] 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.

HIV Testing Schedule for 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 ARV Guidelines identify two levels of HIV acquisition risk for infants: low risk and higher risk.\[16\] For these two levels, higher risk is defined as infants born to mothers living with HIV who met any of the following criteria:\[16\]

- 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 during pregnancy
- Had detectable HIV viral loads close to the time of delivery
- Received combination antiretroviral therapy drugs, but did not have sustained viral suppression (defined as Viral suppression is defined as HIV RNA less than 50 copies/mL).

**Testing Schedule for Infants at 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.\[16\] 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.\[16\]

**Testing Schedule for Infants at Higher Risk**
In addition to the time points above, for infants considered to be at higher-risk of perinatal HIV transmission and those receiving combination antiretroviral prophylaxis, additional virologic diagnostic testing is recommended at birth and 2 to 6 weeks after cessation of antiretroviral prophylaxis (usually this is at 8 to 12 weeks of life).[16,17] 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.[16,17] 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 low risk for perinatal HIV transmission.[17]

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.[16,17]

Exclusion of HIV Diagnosis

The diagnosis of HIV can be excluded in a non-breastfed infant with (1) two negative virologic tests (one at age 1 month or older and another at age 4 months or older) or (2) two or more negative antibody tests performed at 6 months of age or older.[16,17] Some experts also confirm the absence of HIV in a child with a prior negative virologic test by performing an antibody test at 12 to 18 months of age.[16,17] Infrequently, 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.[16,17]

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 infection using the age-appropriate diagnostic testing.[20]

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.[21] 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.[21] A positive screening test followed by a negative differentiation test warrants further testing with an HIV RNA assay.[21] 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 should have a complete medical history, physical examination, and laboratory evaluation.[22] 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.[23, 24, 25] Baseline laboratory evaluation for all children diagnosed with HIV at entry into care should include the following:[22]

- 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 previously demonstrated
- HLA-B*5701 test (if abacavir is being considered as part of the initial antiretroviral therapy regimen)

Routine Monitoring

In general, all children living with HIV should undergo regular evaluation for growth and development, clinical signs and symptoms.

- **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.[22]

- **Monitoring of Children after Initiating Antiretroviral Therapy**: After initiating 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 clinical evaluation and adherence evaluation; the 2 to 4 week visit should also include testing for an HIV RNA level, complete blood count with differential and chemistries. For children maintained on antiretroviral therapy, regular monitoring should 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 if needed.[22] Urinalysis, lipid panel, and random plasma glucose should be obtained every 6 to 12 months.[22]

- **Long-Term Monitoring of Children on Antiretroviral Therapy**: The long-term monitoring of children on antiretroviral therapy should typically occur every 3 to 4 months as outlined above in the monitoring of children after initiating antiretroviral therapy. 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, with HIV RNA levels less than 50 copies/mL, and (3) have a CD4 count above the threshold for opportunistic infection risk.[22]

- **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.[22] 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.[26, 27]

- **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 appropriate further evaluation, such as adherence assessment and genotypic drug resistance testing in the setting of virologic failure.[22]

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. It is conceptually 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.[28] 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.[22]
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.[29,30,31,32] 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.[32] 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.[32,33,34,35,36] 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.[37,38] Several studies have shown that initiating antiretroviral therapy is associated with decreased systemic inflammation, lower risk of cardiomyopathy, and improved neurocognitive outcomes.[39,40,41]

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 ARV Guidelines now recommend rapid initiation of combination antiretroviral treatment for all children diagnosed with HIV infection, regardless of age, CD4 count, or HIV RNA level.[42] 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.[43] 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.[42] 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.[42]

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, including gestational age, or special circumstances.[43,44]

- **Recommendations for Premature Infants**: Due to limited dosing and safety data, zidovudine, lamivudine, and nevirapine are the only antiretroviral medications currently recommended for use in prematurely born infants who are less than 37 weeks gestational age.

- **Recommendations for Infants Born after 37 Weeks Gestation**: 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 (INSTI) ([Table 2]).[44] 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.

- **Choice of Anchor Drug for Infant Antiretroviral Regimen**: 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.[45,46,47,48,49] The tolerability and cleaner profile of the INSTIs make this class particularly appealing in the treatment of pediatric HIV. Recommendations for specific preferred and alternate regimens change frequently as pharmacokinetic and safety data in infants and children become available.
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. 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. 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.

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. The Pediatric ARV Guidelines emphasize 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. These strategies are organized in three categories: (1) initial intervention strategies, (2) medication strategies, and (3) follow-up intervention strategies. To promote adherence, the Pediatric ARV Guidelines recommend regular viral load monitoring and at least one other measure of medication adherence.

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. 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; and rash and hypersensitivity reactions. 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.
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 vaccines based on medical conditions.[59,60,61]

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 for additional vaccinations, including the pneumococcal polysaccharide vaccine (PPSV23) and *Haemophilus influenzae* type b (Hib) vaccine if these vaccines were not administered in infancy.[62]
- 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.[61]
- The CDC and ACIP recommend that adolescents with HIV, regardless of CD4 count or percentage, should receive one dose of the tetanus, diphtheria, acellular pertussis (Tdap) vaccine at age 11 or 12.[61] The Tdap dose at age 11 or 12 should be given regardless of the interval from the last tetanus- and diphtheria-toxoid-containing vaccine.[61]

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 a total CD4 count less than 200 cells/mm$^3$).[61]

- **Live Influenza Virus Vaccine**: The live attenuated influenza vaccine is not recommended for children and adolescents living with HIV, regardless of CD4 cell count or percentage.[61]
- **Live Measles Mumps-Rubella (MMR) Vaccine**: This vaccine is recommended for children or adolescents with HIV with low-level or no immunosuppression, but should not be administered with high-level immunosuppression.[61]
- **Live Rotavirus Vaccine**: Although rotavirus is a live vaccine, it is recommended (with precaution) for all children living with HIV, according to the usual dosing schedule.[61]
- **Live Varicella Vaccine**: This vaccine is recommended for children or adolescents with HIV with low-level or no immunosuppression, but should not be administered with high-level immunosuppression.[61]
- **Zoster Vaccine Live (ZVL)**: The zoster vaccine live (ZVL) is not recommended for use in children or adolescents living with HIV at any age because the amount of live varicella-zoster virus in the ZVL vaccine is more than 10-fold higher than with the varicella vaccine.[59,63]
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 Opportunistic Infection Guidelines provides detailed information regarding prevention and treatment of the major opportunistic infections that occur in children.[64] 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.[65,66,67] 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 Opportunistic Infection Guidelines.[64]

Pneumocystis Pneumonia Prophylaxis

Prophylaxis against Pneumocystis jirovecii pneumonia (PCP) is an extremely beneficial intervention among infants with HIV, especially for those infants not yet on antiretroviral therapy. The highest incidence of PCP in children with HIV occurs during the first year of life, with cases peaking at 3 to 6 months of age.[66] In resource-limited settings, PCP has been shown in autopsy studies to cause up to 44% of HIV-associated deaths in children with HIV.[68]

Initiating Pneumocystis Pneumonia Prophylaxis in Children

The Pediatric Opportunistic Infection Guidelines recommend administering PCP prophylaxis in children with HIV who meet the following age-specific requirements:[66]

- **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/mm$^3$ or CD4 percentage is less than 15%.
- **Age 6 to 12 years:** CD4 count less than 200 cells/mm$^3$ 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.[66] 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.[66] 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 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 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.[66] 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.[65]
Indications for Prophylaxis Against *Toxoplasma* in Children

The Pediatric Opportunistic Infection Guidelines recommend administering *Toxoplasma* encephalitis prophylaxis in toxoplasma-seropositive children with HIV who meet the following age-specific thresholds:[65]

- **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.[65] For those unable to take trimethoprim-sulfamethoxazole, the acceptable alternative is dapsone plus atovaquone.[65] 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.[65] 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.[65]

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:[67]

- **Children aged less than 1 year**: CD4 less than 750 cells/mm³
- **Children aged 1 to less than 2 years**: CD4 less than 500 cells/mm³
- **Children aged 2 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).[67] 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.[67] 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.[67] 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 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.
- In the United States, at year-end 2018, an estimated 1,912 children younger than age 13 were living with diagnosed HIV in the United States.
- 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, 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.
- 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


6. Ryan White & Global HIV/AIDS Programs. A living history. [History of Ryan White Care Act] -


References


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antibody results in HIV-infected children when suppressed. AIDS. 2015;29:1053-60. [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] -


Figures

Figure 1 Annual Number of Live-Born Infants with Perinatal HIV Infection, United States, 1978-2018

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

Figure 2 Persons Living with Diagnosed HIV Infection in United States, by Age, Year End 2018

At year-end 2018, among the 1,025,744 persons living with diagnosed HIV, 1,912 (0.19%) were younger than age 13.

Figure 3 Children Younger Than 13 Years of Age Living with Diagnosed HIV in United States, 2014-2018

Figure 4 Number of Children Younger Than 13 Years of Age Living with Diagnosed HIV, by Race/Ethnicity, United States, Year End 2018

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 6 weeks after cessation of antiretroviral prophylaxis (i.e. at 8–12 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 1.

### HIV Infection Stage\(^a\) Based on Age-Specific CD4 Cell Count or Percentage

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;1 Year</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>&gt;1,500</td>
<td>≥34</td>
<td>&gt;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>

\(^a\)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

## Antiretroviral Regimens Recommended for Initial Therapy in Children

### Preferred Regimens

| Infants, Birth to <14 Days\(^a,b\) | 2NRTIs plus Nevirapine |
| Children Aged ≥14 Days to <3 Years | 2NRTIs plus Lopinavir-ritonavir |
| Children Aged ≥3 Years (weight <25 kg) | 2NRTIs plus Raltegravir\(^c\) (weight ≥2 kg) |
| Children Aged ≥3 Years (weight ≥25 kg) | 2NRTIs plus Atazanavir plus Ritonavir |
| Children Aged ≥3 Years (weight ≥25 kg) | 2NRTIs plus twice daily Darunavir\(^d\) plus Ritonavir |
| Adolescents Aged ≥12 Years with SMRs 1-3 (weight ≥25 kg) | 2NRTIs plus Dolutegravir\(^e\) |
| Adolescents Aged ≥12 Years with SMRs 4 or 5 | Refer to the Adult and Adolescent Antiretroviral Therapy Guidelines |

### Alternative Regimens

| Children Aged ≥14 Days to <3 Years | 2NRTIs plus Nevirapine\(^h\) |
| Children Aged ≥3 Months to <3 Years | 2NRTIs plus Atazanavir plus Ritonavir |
| Children ≥3 Years (weight ≥20 kg to <25 kg) | 2NRTIs plus Dolutegravir\(^g\) |
| Children Aged ≥3 Years (weight ≥25 kg) | 2NRTIs plus Atazanavir plus Ritonavir |
| Children Aged ≥3 Years | 2NRTIs plus Raltegravir\(^c\) |
| Children Aged ≥3 Years | 2NRTIs plus Efavirenz\(^f\) |
| Children Aged ≥6 Years to <12 Years (weight ≥25 kg) | 2NRTIs plus Bictegravir\(^g\) |
| Adolescents Aged ≥12 Years with SMRs 1-3 and weight ≥35 kg | 2NRTIs plus Rilpivirine\(^c\) |
| Adolescents Aged ≥12 Years with SMRs 1-3 and weight ≥40 kg | 2NRTIs plus Atazanavir-cobicistat |
| Adolescents Aged ≥12 Years with SMRs 4 or 5 | Refer to the Adult and Adolescent Antiretroviral Therapy Guidelines |

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

| Children, Birth to Age <3 Months | Zidovudine plus (Lamivudine or Emtricitabine) |
| Children Aged ≥3 Months and <6 Years | Abacavir plus (Lamivudine or Emtricitabine)\(^o\) |
| Children and Adolescents Aged ≥6 Years and SMR 1-3 | Tenofovir alafenamide-Emtricitabine (only if weight ≥25 kg and receiving a regimen that contains an integrase strand transfer inhibitor or a non-nucleoside reverse transcriptase inhibitor)\(^n\) |
| Adolescents Aged ≥12 Years and SMRs of 4 or 5 | Refer to Adult and Adolescent Antiretroviral Therapy Guidelines |
## 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 SMRs of 1-3</td>
<td>Zidovudine plus (Lamivudine or Emtricitabine)</td>
</tr>
</tbody>
</table>

*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.*

*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.*

*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.*

*Darunavir should only be used in children weighing ≥10 kg. Once-daily darunavir 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 and weighing ≥25 kg because there are options that can be administered once-daily. Note that darunavir plus ritonavir can be administered once daily in adolescents aged ≥12 years and weighing ≥40 kg who are not sexually mature (SMR 1-3).*

*A fixed-dose concentration tablet (dolutegravir-abacavir-lamivudine) is available for children who weigh ≥25 kg.*

*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 ≥25 kg.*

*Bictegravir is currently recommended only in fixed-dose combination tablets. Tablets containing bictegravir-emtricitabine-tenofovir alafenamide are recommended as Preferred regimen for adolescents aged ≥12 years and weighing ≥25 kg and as an Alternative regimen for children aged ≥6 and weighing ≥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.*

*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.*

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

*Darunavir-cobicistat is available as part of a fixed-dose combination tablet containing darunavir-cobicistat-emtricitabine-tenofovir alafenamide that has been approved by the FDA for use in children and adolescents weighing ≥40 kg.*

*A fixed-dose combination tablet that contains zidovudine-lamivuduine is available for use in children weighing ≥30 kg.*
A fixed-dose combination tablet that contains abacavir-lamivudine is available for use in children weighing ≥25 kg.

Tenofovir alafenamide-emtricitabine plus a boosted protease inhibitor 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 14, 2020. [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>Description</th>
<th>Routine Assessment of Medication Adherence in Clinical Care</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>

Targeted Approaches to Monitor Adherence in Special Circumstances

<table>
<thead>
<tr>
<th>Description</th>
<th>Targeted Approaches to Monitor Adherence in Special Circumstances</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>

Approaches to Monitor Medication Adherence in Research Settings

<table>
<thead>
<tr>
<th>Description</th>
<th>Approaches to Monitor Medication Adherence in Research Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure drug concentrations in hair.</td>
<td>Good measure of adherence over time.</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 14, 2020. [HIV.gov]