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PEDIATRIC PALLIATIVE CARE FOR YOUTH WITH HIV/AIDS: A SYSTEMATIC REVIEW

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Abstract

Improvement in treatment has led to decreased death in youth with human immunodeficiency virus (HIV) in developed countries. Despite this, youth with HIV are still at risk for increased mortality and morbidity compared with their uninfected counterparts. In developing countries, high numbers of youth die from acquired immune deficiency syndrome (AIDS)-related illnesses due to lack of access to consistent anti retroviral treatment. As a result, pediatric palliative care is a relevant topic for those providing care to youth with HIV. A systematic review was conducted to gather information regarding the status of the literature related to pediatric palliative care and medical decision-making for youth with HIV. This review article focused primarily on physical aspects of care, with less attention paid to psychological, social, ethical, and cultural aspects of care. It recommends that future research focuses on broadening the evaluation of pediatric palliative care among youth with HIV by directly evaluating the psychological, social, ethical, and cultural aspects of care and investigating the needs of all involved stakeholders.

Keywords: human immunodeficiency virus, acquired immune deficiency syndrome, anti retroviral, pediatric palliative care.

Introduction:

HIV (human immunodeficiency virus) and AIDS (acquired immunodeficiency syndrome) are often spoken of as the same, but they are not:

- HIV is a virus that attacks the body's immune system and weakens its ability to fight off infection.

- AIDS is an advanced stage of HIV infection in which the immune system is so weak that patients are likely to get infections and/or cancers that typically do not affect people with normal immune systems.[1]
- So, while every patient with AIDS has an HIV infection, not all HIV-infected patients have AIDS. Early diagnosis and treatment of HIV infection can prevent patients from getting AIDS.[2]

History:

Ideally, the diagnosis of HIV in a child is made through perinatal testing. The Centers for Disease Control and Prevention (CDC) has issued guidelines for recommended testing and counseling for all pregnant women; however, many women, especially in developing countries and in poorer areas of the developed world, do not have access to or do not avail themselves of the resources available. Thus, for example, the diagnosis of HIV infection may follow an investigation of a prolonged or unusual presentation of an infection or a malignancy.

Some studies suggest that children vertically infected with HIV become symptomatic from the neonatal period up to age 8 years and that 57% of this group have associated disease within the first year.[3]

Children infected as a result of sexual abuse or drug use may not present with known HIV infection.

Immunodeficiency should be suspected in individuals with recurrent bacterial infections (especially invasive infections, eg, bacteremia, meningitis, and pneumonia) and in those with unusual infections, such as those caused by the*Mycobacterium avium-intracellulare* complex (MAC).

Children with HIV infection often present with the common bacterial infections of childhood (eg, otitis media, sinusitis, pneumonia). These can be more frequent and more severe than similar infections in immunologically healthy children. Recurrent fungal infections, such as candidiasis (thrush), that do not respond to standard antifungal agents suggest lymphocytic dysfunction.[4]

Recurrent or unusually severe viral infections, such as recurrent or disseminated herpes simplex or zoster infection or cytomegalovirus (CMV) retinitis, are seen with moderate-to-severe cellular immune deficiency.

Growth

Growth failure, failure to thrive, or wasting in a child may indicate HIV infection if other common metabolic and endocrine disorders do not appear to be the etiologies. Growth failure, failure to thrive, or wasting in a patient with HIV infection may signify disease progression or underlying malnutrition.[5]

Development

Failure to attain typical milestones suggests a developmental delay. Such delays, particularly impairment in the development of expressive language, may indicate HIV encephalopathy. The loss of previously attained milestones may signify a CNS insult due to progressive HIV encephalopathy or opportunistic infection.

In older children, behavioral abnormalities (eg, loss of concentration and memory) may indicate HIV encephalopathy.[6]

Practice Essentials: Since the first cases of human immunodeficiency virus (HIV) infection were identified, the number of children infected with HIV has risen dramatically in developing countries, the result of an increased number of HIV-infected women of childbearing age in these areas. HIV is a retrovirus and can be transmitted vertically, sexually, or via contaminated blood products or IV drug abuse. Vertical HIV infection occurs before birth, during delivery, or after birth.

In a study of HIV-1-infected, highly active antiretroviral therapy (HAART)-naive children, Yin et al found that beginning HAART at younger ages and healthier CD4 levels results in better immune recovery.[7,8] In all, 72% of children who were immunosuppressed at baseline recovered to normal within 4 years after initiating HAART therapy. Compared with children with severe immunosuppression, more children with mild immunosuppression (+36%) or advanced immunosuppression (+20.8%) recovered a normal CD4 percentage.

For every 5-year increase in baseline age, the proportion of children who achieved a normal CD4 percentage fell by 19%.[8] Combining age effects and baseline CD4 percentage resulted in more than 90% recovery when HAART was initiated in children with mild immunosuppression at any age or advanced immunosuppression at an age younger than 3 years. Most of the immunologic benefits of HAART remained significant at 4 years.

Background:

Over the past 30 years, since the first cases of what is now recognized as human immunodeficiency virus (HIV) infection were identified in 1981, the number of children infected with HIV has increased dramatically in developing countries because the number of HIV-infected women of childbearing age has risen.

However, great advances have been made in the United States and in other industrialized nations to control transmission of the virus from mother to infant.

In the United States, universal prenatal HIV testing has been recommended to obstetricians since 1995. However, this testing was not mandatory in all states. Before prenatal testing was common, diagnosing HIV infections in a woman

after diagnosing it in her child was not unusual, and the diagnosis of acquired immunodeficiency syndrome (AIDS) in a previously healthy child was not rare.[9]

Before 1985, one way in which children were infected was the transfusion of blood-products. Improved screening tests have essentially eliminated such transmission. A common way adolescents become infected is by engaging in high-risk behaviors such as unprotected sexual intercourse and injection drug abuse.

Surveillance data now show that the only group with increasing HIV incidence is men who have sex with men. The proportion of this population who are unaware of their infection is high, with unawareness among young men (18-29 y) reaching 63%.[10]

In the United States, youths aged 13-24 years accounted for 25.7% of new HIV infections in 2010.[11]

In pediatric patients, HIV infection progresses as it does in adults, although surveillance data from the Centers for Disease Control and Prevention (CDC) suggest that patients who are aged 13-24 years when diagnosed with AIDS survive longer than older individuals do. Vertically transmitted HIV can cause rapidly progressive, chronically progressive, or adultlike disease in which a significant clinical latency period occurs before symptoms appear.

The World Health Organization (WHO)[12] estimates that approximately 2.5 million children were living with HIV infection as of 2009. In 2009 alone, 370,000 children were newly infected.[7] This is a drop of 24% from 5 years earlier.[13]

Not only are the children themselves ravaged by disease, but their primary caregivers have also often succumbed to AIDS. This is most prevalent in sub-Saharan Africa, where an estimated 11.6 million children had been orphaned by AIDS as of 2007.

Although 2 strains of HIV have currently been identified, most patients who have AIDS are positive for HIV type 1 (HIV-1) or are positive for both HIV-1 and HIV type 2 (HIV-2). HIV-2 infection is most commonly observed in West Africa.

Other routes of transmission, such as transfusion of blood and blood components, are rare in the United States but still exist in developing countries. Sexual abuse of children and high-risk behaviors in adolescents also contribute to youth HIV infection.[14]

Pathophysiology:

HIV can be transmitted vertically, sexually, or via contaminated blood products or IV drug abuse. Vertical HIV infection occurs before birth, during delivery, or after birth. With infection before birth (period 1), the fetus can be hematologically infected by means of transmission across the placenta or across the amniotic membranes, especially if the membranes are inflamed or infected.

Most vertical infections occur during delivery (period 2), and many factors affect the risk of infection during this period. In general, the longer and the greater amount of contact the neonate has with infected maternal blood and cervicovaginal secretions, the greater the risk of vertical transmission. Premature and low-birthweight neonates appear to have an increased risk of infection during delivery because of their reduced skin barrier and immunologic defenses.[15]

Postnatal vertical transmission (period 3) occurs with the ingestion of HIV in the breast milk.

HIV Virology

HIV is a retrovirus. Structurally, a lipid bilayer envelope surrounds the cylindrical core of HIV, which contains the RNA genetic information and the machinery that promotes viral replication and integration during initial cellular infection. From the outside, the virion appears spherical, with a diameter of 110 nm.

HIV has a variety of structural and nonstructural proteins that determine the interaction of the virus with the host's immune system and cellular components.

The HIV virus attaches to the host cell by the association of a surface glycoprotein to the CD4 molecule; therefore, it primarily infects $CD4^+$ lymphocytes and macrophages. After HIV enters a host, trimeric gp120 glycoproteins that protrude from its lipoprotein bilayer envelope bind to CD4 cell-surface receptors and CCR5 or CXCR4 chemokine co-receptors. Juxtapositioned co-receptors are needed for viral infection. The V3 region of the gp120 glycoprotein determines cellular tropism, and tropism is involved in syncytial formation.[16] Tropic (nonsyncytial) strains prefer the CCR5 co-receptor and are the primary causes of infection. Upon entering the cell, the protease enzyme produces the reverse transcriptase and ribonuclease (RNAse) H enzymes responsible for synthesizing the single-stranded DNA (ssDNA) molecules and primers necessary to produce the complementary DNA strand. Because reverse transcriptase lacks proofreading capacity, considerable base-to-base variability results. The high mutation rate, combined with the high reproductive rate, results in substantial evolution and subsequent resistance to treatment.[17]

Once the virus core enters the cell cytoplasm of the host, viral reverse transcriptase copies viral RNA to the DNA of the host. The viral DNA is then transported into the nucleus and incorporated into the DNA of that cell. If activated, viral expression can result in new viral RNA and proteins. New viral core proteins, enzymes, and viral RNA molecules can induce budding, with additional cell infection.[18]

Immune response: Acute infection rapidly increases the viral load and causes a mild-to-moderate viremia. Although viral loads tend to diminish rapidly after acute infection in adults, they decrease slowly in vertically infected children and may not reach baseline levels until age 4-5 years. Although infants possess numerous antigen-presenting and effector cells compared with adults, their cytokine production, proliferation, and cytotoxicity are reduced.

Envelope-specific cytotoxic T-lymphocytes are less common in children who vertically acquire the disease than in children who acquire HIV by means of blood transfusion. Among those with vertically acquired disease, such lymphocytes are least common in those with rapidly progressing disease.[19] Precursors of cytotoxic T-lymphocyte that are specific to HIV type 1 (HIV-1) do not develop in significant number until the child is aged 1 year.

The reduction in cell-mediated immunity and secondary B-cell dysfunction result in the immunocompromised state and in the proliferation of opportunistic infections and malignancies. An elevated level of activation-induced cell death resulting from apoptosis of T cells occurs in patients who are HIV positive.

The CD95/Fas receptor/ligand system is necessary for the apoptosis of T cells, and abnormalities in this system are linked with increased T-cell death in patients who are HIV positive. As the immune status deteriorates, an increase in $CD95^+$ T cells is found; conversely, a low $CD95^+$ T-cell count is found in asymptomatic patients who are HIV positive.[20]

Haematopoietic effects

Although HIV infects hematopoietic stem cells, the importance is minor. Hematopoietic disturbances are believed to occur as a consequence of changes in the microenvironment of the marrow and of deficiencies in local and systemic growth factors.

In typical conditions, the stroma of the marrow promotes stem cell proliferation and differentiation by producing granulocyte colony-stimulating factor (G-CSF) and interleukin (IL)-3. HIV-infected stroma produces less G-CSF and IL-3 than normal and produces excessive tumor necrosis factor (TNF)-alpha and IFN-gamma. This cytokine

dysregulation halts the production of badly needed hematopoietic cell lines and causes apoptosis of committed progenitor cells.[21]

HIV also appears to retard the production of thrombopoietin in the liver and erythropoietin in the kidney. In addition to a low serum erythropoietin level, HIV-induced anemia is also a result of a blunted response to erythropoietin.

The etiology is probably multifactorial in most patients. Common contributing factors are bone marrow suppression, iatrogenic causes, vitamin deficiencies, suppressed erythropoietin production, and a blunted erythropoietin response. Bone marrow infiltration with lymphoma or Kaposi sarcoma may be noted. Bone marrow suppression may be due to pathogens such as MAC, parvovirus B19, or CMV. Disseminated fungemia can cause anemia.

Neutropenia is observed in 10% of patients with early asymptomatic HIV infections and in 50% of patients with AIDS. Neutropenia results from the aforementioned mechanisms, as well as from medication.[22,23] Granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF deficiencies not only reduce neutrophil production but also reduce granulocytic and monocytic function. GM-CSF and G-CSF promote increased neutrophilic function, including superoxide production, phagocytosis, intracellular killing, and antibody-dependent cellular cytotoxicity.

Neurologic effects

HIV exhibits tropism for the CNS, especially the microglia. As many as 10% of children with AIDS have progressive encephalopathy. Progressive white matter degeneration and brain atrophy may develop. Neurologic symptoms develop along with developmental delay.[23]

Viral resistance

In terms of the mechanisms of resistance development, the rapid turnover rate and high error rate of reverse transcriptase induces 3300 new single mutations per day. When a mutation improves the survival of the virus in an existing drug environment, that quasispecies is selected to reproduce. The higher the viral load and the higher the rate of replication, the greater the number of resistant quasispecies. Quasispecies can be transmitted to a fetus or neonate.

HIV resistance develops because of low antiretroviral drug (ARD) levels due to several factors including variations in drug absorption and metabolism and noncompliance because of adverse effects or a poor understanding of the importance of the medication.[24] Viral sanctuary sites may be exposed to low levels of ARDs, and resistant quasispecies may develop.

Etiology:

Infection is due to HIV, a complex member of the Lentivirus genus of the Retroviridae family. HIV-1 is the most common cause of HIV infection in the Americas, in Europe, in Asia, and in Africa. HIV-2 has caused epidemics in West Africa, although this virus is also found in European countries. HIV-2 disease progresses more slowly than HIV-1 disease, and HIV-2 is less transmissible than HIV-1.

HIV-1 subtypes differ by geographic region. HIV-1 subtype B is predominant in the United States. Non-B subtypes are particularly prevalent in Africa and Asia.[25] The high transmission rate from Africa to Europe has increased the diversity of subtypes in Europe. Non-B subtype HIV-1 infections are increasing in the United States.

Vertical transmission of HIV from mother to child is the main route by which childhood HIV infection is acquired; the risk of perinatal acquisition is 25%. African epidemiologic data of almost 2000 infants indicate that female infants may be more susceptible to HIV infection before birth and continuing after birth compared with male infants.[26]

Epidemiology:

US Statistics

The HIV seroprevalence rate in pregnant women is as high as 0.3%. The seroprevalence of women infected with HIV is highest in the Northeast, followed by the South. Perinatal HIV transmission rates are 25% but as low as 2% in untreated women with viral loads of less than 100 copies/mL.

Although prophylactic interventions have reduced vertical transmissions, cases of perinatal HIV transmission continue to occur.[27] This is largely because of missed opportunities for prevention, particularly among women who lack prenatal care or who are not being offered voluntary HIV counseling and testing during pregnancy. In many as 40% of the mothers of infants with perinatally acquired HIV infection, the HIV infection was not known before delivery.

The CDC estimates that in 2009, in those 40 states, the number of pediatric HIV infections diagnosed was as follows[28] :

- Under age 13 years: 166
- Ages 13-14 years: 21
- Ages 15-19 years: 2036

In 2009, 12 cases of perinatally transmitted late HIV disease (AIDS) were diagnosed. The estimated cumulative number of perinatally transmitted AIDS cases diagnosed through 2009 is 8640.

At the end of 2008, 3022 children younger than 13 years were living with HIV infection in the 40 states with confidential name-based HIV infection reporting.

In 2007, 19 US children younger than 15 years died of HIV disease.[29] These numbers are in stark contrast to what is occurring internationally.

Adolescents and young adults

CDC HIV surveillance statistics from 2010 report that 25.7% (approximately 12,200 individuals) of new cases of HIV infection in the United States are in adolescents and young adults aged 13-24 years. Males accounted for 82.8% of new cases of HIV infection among this age group. Of these, 7,000 (57.4%) were African Americans, 2,390 (19.6%) were Latino, and 2,380 (19.5%) were white. Male-to-male sexual contact accounted for 72.1% (8,800 individuals).[30,31] The percentage of youths tested for HIV infection was 12.9% in high-school students and 34.5% in individuals aged 18-24 years. Testing rates were lower in males than in females. More than half (59.5%) of youths with HIV infection are unaware of their infection.[31]

International statistics

The WHO estimates that over 33 million individuals are infected with HIV worldwide, and 90% of them are in developing countries. HIV has infected 4.4 million children and has resulted in the deaths of 3.2 million. Each day, 1800 children—the vast majority newborns—are infected with HIV. Approximately 7% of the population in sub-Saharan Africa is infected with HIV; these individuals represent 64% of the world's HIV-infected population. Furthermore, 76% of all women infected with HIV live in this region.

Globally, children outside the United States are not faring as well. Every day, 1400 children become HIV positive and 1000 children die of HIV-related causes. An estimated 2.5 million children worldwide younger than 15 years are living with HIV/AIDS.

In sub-Saharan Africa alone, 1.9 million children are living with HIV/AIDS and more than 60% of all new HIV infections occur in women, infants, or young children. As of 2007, 90% of the newly infected children are infants who acquire HIV from their infected mothers.[32] Alarmingly, 90% of babies who acquire the disease from infected mothers are found in sub-Saharan Africa. The prevalence of HIV infection among undernourished children has been estimated to be as high as 25%.

A 2006 South African study estimated that HIV/AIDS is the single largest cause of infant and childhood deaths in rural South Africa.[33] HIV/AIDS is now responsible for 332,000 child deaths in sub-Saharan Africa, almost 8% of all child deaths in the region.

Racial differences

Black and Hispanic children are disproportionately infected in the United States. As of 2002, HIV infection was the 7th and 10th leading cause of death in black children and in Hispanic teens, respectively.[34] Approximately 62% of children with AIDS are black.

In the United States, children from minority communities have been most affected by AIDS. More than 50% of infected children are black, and slightly less than 25% are Hispanic. Of the new childhood HIV cases in 2003, 68% occurred in African Americans. The number of pediatric AIDS cases reported in black non-Hispanic children is 3.4 times higher than in white non-Hispanic children and is 2.6 times higher than that of Hispanic children.[35]

Sexual differences

Women of childbearing age are one of the fastest growing groups with AIDS; 20% of AIDS cases in adults in the United States occur in this group.

Young people (aged 15-44 y) account for one of the fastest growing infected groups and account for almost half of all infections. Among young people, young women are more likely to become infected. In sub-Saharan Africa, more than two thirds of all youth infected are young girls.[36] Variations in frequencies in the sexes in other regions of the world depend on the predominance of commercial sex workers and the proportion of a transient and mobile workforce more likely to be separated from family.

Age-related differences

Because vertical transmission from mother to child is the main route by which pediatric HIV infection is acquired, most children who are HIV positive should be identified in infancy. Although current treatment strategies can prevent vertical transmission, the drugs are simply not available in many places, especially in Africa.

The following factors are associated with rapidly progressive disease in infants[37]:

- Advanced maternal disease
- High maternal viral load

- Low maternal CD4 $^{+}$ count
- Prematurity
- In utero transmission
- High viral load in the first 2 months of life
- Lack of neutralizing antibodies
- Presence of p24 antigen
- AIDS-defining illnesses
- Early cytomegalovirus (CMV) infection
- Early neurologic disease
- Failure to thrive
- Early-onset diarrhea

Each logarithmic decrease in the viral load after the start of therapy decreases the risk of progression by 54%.

Baseline HIV RNA copy number (copies/mL) and associated intermediate-term risk for death in HIV-infected children is as follows[38]:

- Undetectable (ie, ≤4,000): 24%
- 4,001-50,000: 28%
- 50,001- 100,000: 15%
- 100,001- 500,000: 40%
- 500,001-1,000,00: 40%
- 1,000,000: 71%

The natural progression of vertically acquired HIV infection appears to have a trimodal distribution. Approximately 15% of children have rapidly progressive disease, and the remainder has either a chronic progressive course or an infection pattern typical of that observed in adults. Mean survival is about 10 years.

Physical Examination:

A high percentage of oral disease has been seen in children infected with HIV, and oral manifestations are often early indicators of infection. Numerous mucocutaneous disorders have been reported in children infected with HIV. As the

$CD4^+$ count decreases, an increase in the number and severity of skin manifestations can be expected.[39] Dermatologic manifestations occur more frequently in children with advanced HIV disease; many tend to improve after antiretroviral therapy is initiated.

The most common oral disease and mucocutaneous presentation of HIV infection is candidiasis caused by *Candida albicans*. Both the pseudomembranous variant and the atrophic oral variant are most common.

The usual symptoms in children with candidal esophagitis are odynophagia, dysphagia, and retrosternal pain.[40] These symptoms may contribute to the already-compromised nutritional status of the child.

Candidiasis may manifest as an unresponsive or recurrent diaper rash or as a chronic paronychia and onychomycosis. In *Candida* -associated diaper dermatitis, the area covered by the diaper is usually inflamed and erythematous, with satellite lesions extending beyond the central area of involvement. Involvement of other intertriginous areas, including neck folds and axillary regions, has also been reported. Children infected with HIV have a higher rate of dental caries in the primary teeth but a diminished prevalence in the permanent teeth, a finding attributed to the greater number of primary teeth and the delayed eruption of the permanent teeth in these patients. HIV-infected children should be screened and considered at high risk for dental caries, usually secondary to chronic medication use.[41,42]

Anthropometric findings

Monitoring the patient's growth is one of the most important parts of the pediatric physical examination. Anthropometric measurements should be obtained at each visit. Delayed growth in the head circumference is correlated with the development of underlying encephalopathy. However, normal head growth does not help in ruling out encephalopathy, and many patients with a normal head circumference may have radiographic or psychometric findings consistent with encephalopathy. Diverse diagnostic criteria have been used. Anthropometric measurements, such as skin-fold thickness and the waist-to-hip ratio, are useful to monitor the progression of changes.[43] Technically sophisticated tools include bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), CT, and MRI.

Head, eyes, ear, nose & throat findings

Parotid enlargement is observed in 30% of children with category C disease (see Staging) and in 15% of children with disease in other categories. Thrush in the oral cavity and posterior pharynx is observed in approximately 30% of HIV-

infected children.[44] In children with AIDS, the prevalence of thrush is correlated with a low $CD4^+$ count. Thrush in the posterior pharynx may signify candidal esophagitis, especially in patients with feeding difficulties or retrosternal pain.

Cardiac, pulmonary & abdominal findings

Cardiomyopathy may be present. Congestive heart failure may be present. Lung examination is important, and good documentation of findings is required at each visit. Chronic lung disease may produce baseline findings of crackles and decreased regional breath sounds.

Changes in the lung findings are important to note because pneumonia is common in children with HIV infection.[45] Pneumonia may not be obvious during the examination, and many children have few symptoms. For example, *Mycoplasma*infection may not cause a high temperature, and *Pneumocystis jiroveci* infection may cause only tachypnea, fever, and hypoxemia.

Lymphatic findings

Generalized cervical, axillary, or inguinal lymphadenopathy is common and may be the first sign of initial infection during the asymptomatic phase of the disease. Generalized lymphadenopathy may not be present with well-controlled disease or end-stage AIDS. New shotty nodes may indicate that the disease has again progressed and that treatment failure has occurred.[46]

A single large node may indicate lymphoma, and it may need to be examined with biopsy.

Neurologic findings

Motor delay, hypotonia, hypertonia, and/or pyramidal-tract signs may indicate progressive HIV encephalopathy or opportunistic infection of the CNS. Spastic diplegia and oral motor dysfunction are early signs of encephalopathy. Ischemic and hemorrhagic strokes can occur in children with AIDS, but they seem to be related to infection or other mechanisms other than atherosclerosis or hypercoagulable states, as in the adult HIV-infected population.[47]

Skin findings

HIV dermatitis causes an erythematous papular rash and is observed in about 25% of children with HIV infection. Vesicular lesions in a unilateral dermatomal distribution or in the oral, genital, or anal area may represent reactivation of herpes zoster.

Extremities findings

Digital clubbing may be observed as a result of chronic lung disease. Nonpitting edema may result from hypoalbuminemia caused by HIV nephropathy or malnutrition. Pitting edema may develop as a result of congestive heart failure.

Nephropathy

In approximately 15% and 5% of HIV-infected children with AIDS and those without AIDS, respectively, the disease progresses to HIV nephropathy. HIV nephropathy is more common in African American children than in others.[48]

Proteinuria and hyponatremia with elevation in BUN and creatinine levels and a slight increase in blood pressure develop early and are not uncommon.

Renal biopsy most often reveals focal segmental glomerulosclerosis or, sometimes, mesangial hyperplasia. Necrotizing glomerulonephritis and minimal histologic changes also are observed.

Non-HIV nephropathy may develop, especially in children who are treated with repeat courses of nephrotoxic medications. Some children have chronic renal failure with electrolyte wasting. Electrolyte levels should be monitored closely, and patients should receive appropriate supplementation.[49]

Diagnostic Considerations:

Older children and young teenagers can have human immunodeficiency virus (HIV) infection or AIDS without a history of immunodeficiency or severe illness. Fever of unknown origin, recurrent infection, growth failure, or developmental regression without an obvious etiology should increase the index of suspicion for HIV infection.

The failure to complete neonatal testing is another pitfall. The process to verity that an at-risk neonate does not have HIV infection is complex. Too often, follow-up tests are not performed if initial results are negative.

Prenatal HIV tests are often performed, but the results may not be followed up, especially in low-risk women.[50]

Non opportunistic infections

Like most children, children with HIV are susceptible to common pathogens. Diseases caused by such pathogens should be high in the list of differential diagnoses for these children. Of course, the particular child's medical history guides the differential diagnosis. For example, chronic lung disease requires special consideration of atypical respiratory pathogens, such as *Pseudomonas* or *Xanthomonas* species.

One of the challenges with children who are infected with HIV is that they are more likely than others to have recurrent infections, which cause them to undergo repeat treatment with many broad-spectrum antibiotics.[51] This antibiotic exposure increases the risk of their developing resistant pathogens. Therefore, infection with penicillin-resistant pneumococci is not uncommon in children with recurrent ear infections.

Differential Diagnoses:[52]

- Anemia, Chronic
- Autoimmune and Chronic Benign Neutropenia
- Bruton Agammaglobulinemia
- Common Variable Immunodeficiency
- Constitutional Growth Delay
- Failure to Thrive
- Lymphadenopathy
- Malabsorption Syndromes
- Malnutrition
- Severe Combined Immunodeficiency
- Transient Hypogammaglobulinemia of Infancy

Approach Considerations:

Prompt diagnosis of human immunodeficiency virus (HIV) infection is critical. As such, the Centers for Disease Control and Prevention (CDC) recommends routine prenatal HIV testing as the standard of care for all pregnant women in the United States, with repeat screening in the third trimester recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.[53] However, routine late pregnancy testing at 36-37 weeks' gestation in all women is recommended by many experts because infection during pregnancy now makes up a significant percentage of children with AIDS.

Diagnosis of HIV infection in infants is aided by HIV culture or DNA/RNA polymerase chain reaction (PCR); positive results are confirmed by repeating the test. In suspected cases, HIV testing should occur in the newborn period (i.e, before the infant is 48 h old), at age 1-2 months, and again at age 3-6 months. Testing at age 14 days may allow for

earlier detection of HIV in infants who had negative test results within the first 48 hours of life.[54] By approximately age 1 month, PCR testing has a 96% sensitivity and 99% specificity to identify HIV.

Preferred virologic assays include HIV bDNA PCR and HIV RNA assays.

Further virologic testing in infants with known perinatal HIV exposure is recommended at 14 days, at 1 month, and at 4 months.

An antibody test to document seroreversion to HIV antibody–negative status in uninfected infants is no longer recommended at age 12–18 months

In children 18 months and older, HIV antibody assays can be used for diagnosis.[55]

HIV infection can be ruled out if one of the following is true:

- DNA HIV PCR results are consistently negative in an infant older than 4 months in the absence of breastfeeding.
- Two DNA HIV PCR results obtained at least a month apart are negative in an infant older than 6 months.

Monitor $CD4^+$ levels or percentages in infants or patients newly diagnosed with HIV at 3- to 4-month intervals to assess patients' immune status. In children younger than 5 years, the 2010 Panel recommends using CD4 percentages over absolute CD4 counts for monitoring disease progression because of inherent age-related changes in absolute CD4 counts.[56]

Monitor for opportunistic infections. Perform a CBC count with differential and a urinalysis every 1-3 months in infants. Older children can be screened every 3-6 months (CBC count) or yearly (urinalysis). Culture urine samples monthly for the presence of cytomegalovirus (CMV) until age 2 months and then at 2-month intervals until age 12 months.

Detection of HIV:

HIV detection is the first step in the laboratory workup. In September 2006, the CDC released its Revised Recommendations for HIV Testing of Adults Adolescents, and Pregnant Women in Health-Care Settings.[57] These new recommendations, which replaced the CDC's 1993 Recommendations for HIV Testing Services for Inpatients and Outpatients in Acute Care Hospital Settings, advise routine HIV screening for adults, adolescents, and pregnant women in healthcare settings in the United States. They also recommend reducing barriers to HIV testing. A 2011 revision to the American Academy of Pediatrics (AAP) policy statement recommends that routine screening be offered to all

adolescents at least once by 16 to 18 years of age in communities with high HIV prevalence. In areas of lower prevalence, routine testing is encouraged for all sexually active adolescents and those with other risk factors for HIV.[58]

Detection of antibody to HIV is the usual first step in diagnosing HIV infection. In adults and older children, enzyme-linked immunosorbent assay (ELISA) and Western blotting are used to initially detect HIV-specific antibodies. However, because maternal antibodies are present in neonatal blood, these tests are not used for diagnosis in patients younger than 2 years. A nucleic acid PCR assay is the standard detection method in infants and young children.

HIV DNA PCR is used to detect HIV-1 provirus in mononuclear cells by using oligonucleotides directed at highly conserved regions of the viral genome. This test can be performed within 24 hours of infection and has a sensitivity and a specificity of 95% and 97%, respectively. Although it is more sensitive than viral culturing, the diagnostic performances of the 2 methods are equivalent.[59]

Viral Load Testing:

The viral load can be quantified by using several HIV assays. The number of virions in the peripheral blood is an important indicator of disease activity and of the effectiveness of antiretroviral therapy (ART). A 5- or 3-fold change in the viral load is needed to reliably indicate a clinically significant change in children younger than 2 years or older than 2 years, respectively.

Reverse-transcription PCR (RT-PCR) and nucleic acid sequence—based amplification (NASBA) of plasma RNA reveal a viral load 2 times that obtained with the branched-chain DNA (bDNA) method. The former methods are sensitive to only HIV-1 subtype B viruses,[60] whereas the bDNA method is sensitive to other HIV-1 subtypes. Switching test methods during treatment is not advised because their molecular technologies differ.

Viral Resistance Assays:

Viral resistance to ART may be present. Both primary and secondary mutations can develop. Primary mutations alter the effectiveness of ART. Secondary mutations improve viral survival.

Both genotypic and phenotypic assays can be performed. Genotypic assays are fast and available, but they reveal only known mutations, and they cannot be used to predict complex interactions when several antiretroviral drugs (ARDs) are used together.[61]

Automated recombinant phenotypic assays are commercially available, but the results require additional time to be ready, and the tests are expensive. However, these assays can be used to detect complex interactions between ARDs and quasispecies, to perform in vitro drug trials, and to measure ART inhibitory concentrations.

Hematology Studies:

The $CD4^+$ lymphocyte count is a surrogate marker for disease progression and should be monitored closely. The $CD4^+$ count should be obtained before therapy. A rapid decrease in the count, especially in infants younger than 1 year, is a poor prognostic sign and should prompt the start or alteration of therapy.

Consumptive thrombocytopenia is a common finding in children with HIV infection and may be observed in 10% of patients at initial diagnosis.

Anemia occurs in as many as 20% of patients at diagnosis and occurs in as many as 80% of patients at some time.[62] Anemia can have many etiologies in HIV infected individuals and requires a workup as described in Medical Care.

Blood smears may reveal large ovalocytes and hypersegmented polymorphonucleocytes in cases of folate deficiency.

Other Clinical Laboratory Tests:

Serum electrolytes should be monitored on a regular basis because medications or HIV infection may induce nephrotoxicity.

Liver function can be impaired as a result of medication, HIV, co-infection with hepatitis viruses, or opportunistic infections, so transaminase levels should be monitored. Pancreatitis can be the result of medication, HIV or opportunistic infections, so amylase and lipase levels should be monitored in patients with abdominal symptoms. Parotiditis (parotitis) is not uncommon, and amylase levels should be followed up if parotiditis is suspected or if the patient has a history of the condition. Quantitative immunoglobulin levels should be followed up periodically. Hyperimmunoglobulinemia is associated with disease progression. Hypoimmunoglobulinemia is observed in end-stage disease and is associated with a poor prognosis.[63,64]

Renal Imaging Studies: Patients with HIV nephropathy demonstrate increased size and echogenicity of the kidneys on renal ultrasonography, with a loss of cortical medullary differentiation. Renal cysts are observed with an increased incidence. On renal CT scanning, stasis of urine in the pyramids is observed in patients with HIV nephropathy. This finding, combined with characteristic renal ultrasound findings, is specific for HIV nephropathy.[65]

On renal gallium scanning, increased signal indicates inflammation in patients with HIV nephropathy and is correlated with proteinuria.[65]

Biopsy: A biopsy sample should be taken from enlarged lymph nodes of undetermined cause, especially if they are single, hard, nonmotile, or unaccompanied by generalized lymphadenopathy.

Biopsy may also be considered too clearly determine the identity of an apparently infectious or malignant cutaneous lesion. Maintain a high index of suspicion for a wide array of infections and malignancies, and request the appropriate staining and tissue preparation.[66]

Diagnosis of Lymphoid Interstitial Pneumonitis:

Lymphoid interstitial pneumonitis (LIP) is the second most common AIDS-defining illness in children. LIP most commonly occurs in children with a relatively high $CD4^+$ count. Chest radiography demonstrates a reticulonodular pattern with or without hilar adenopathy that persists for more than 2 months despite treatment.

Patients are usually asymptomatic at first, but cough and shortness of breath develop as lymphoid interstitial pneumonitis progresses. Hypoxia typically responds to a 2-week course of steroids, but oxygen dependence develops if an underlying chronic lung disease exists. Lymphoid interstitial pneumonitis increases the risk of bacterial pneumonia, especially with *Haemophilus influenzae* and pneumococcus.[67]

Recurrent pneumonia destroys lung tissue and leads to chronic lung disease. Chest radiographs demonstrate chronic changes, including areas of chronic atelectasis. This condition requires management by a pulmonologist. Chronic respiratory therapy may be required, including home oxygen therapy.

Staging:

Clinical categories are based on the 2010 CDC guidelines for antiretroviral treatment of pediatric AIDS (review and modification of the 1994 CDC HIV pediatric classification system for clinical categories in children younger than 13 y). This system uses a clinical-category letter and an immunologic number to note each stage of disease progression. The clinical categories are based on clinic manifestations. The immunologic category is based on the age-dependent $CD4^+$count.

Clinical categories include the following:[68]

N – Not symptomatic

A – Mildly symptomatic

B – Moderately symptomatic

C – Severely symptomatic.

Category N includes children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A includes children with 2 or more of the following conditions but none of the conditions listed in categories B and C:

Category B includes children who have symptomatic conditions, other than those listed for category A or category C, that are attributed to HIV infection.

Category C includes children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP (which is a category B condition).[69]

Overview of Anti retroviral Therapy:

Nearly 30 anti retroviral drugs have been approved for use in adults and adolescents with HIV; 18 of these have an approved pediatric treatment indication, and 15 are available as a pediatric formulation or capsule size. Classes of anti retroviral agents include the following:

- Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Fusion inhibitors
- CCR5 co-receptor antagonists (entry inhibitors)
- HIV integrase strand transfer inhibitors

The reverse transcriptase inhibitors (NRTIs, NNRTIs) suppress HIV replication by competitive inhibition of viral reverse transcriptase.[70] PIs prevent the late stages of viral replication by interfering with the formation of structural proteins of the virion core.

Treatment guidelines

Recommended treatment regimens are constantly modified and changed; any publication like this article may become quickly outdated. Therefore, this article is intended to be a primer, and all children should be referred to a pediatric infectious specialist for management. Most patients with vertically acquired HIV are treated regardless of their immune status. Most infants younger than 1 year should be aggressively treated. Pediatric HIV experts agree that infected infants who have clinical symptoms of HIV disease or evidence of immune compromise should be treated. Patients aged 1 year or older with AIDS or significant symptoms should be aggressively treated regardless of CD4 percentage and count or plasma HIV RNA level. A study by Cotton et al found that fosamprenavir/ritonavir–containing regimens in HIV-infected children aged 4 weeks to 2 years achieved plasma amprenavir exposures comparable to those of regimens approved in adults (except for trough exposures in infants under age 6 months). Viral suppression was achieved in 61% of patients, and the regimens were generally well tolerated, with the most common adverse events being diarrhea, upper respiratory tract infection, gastroenteritis, and otitis media.[71]

Monitoring therapy

Close monitoring to determine whether the child is tolerating ART and to answer any questions the caregiver may have are essential to the success of these therapies. At 4-8 weeks after the start of therapy, the $CD4^+$ count and/or percentage and HIV RNA levels should be reassessed, and laboratory evaluations for toxicity should be done. The main goal of therapy is to lower HIV RNA to undetectable levels, although not all infants achieve this. Some have a 10-fold or 5-fold decrease in the viral load.[67]

Treatment failure

Treatment failure is defined as virologic, immunologic, or clinical.[72] Virologic failure includes incomplete response and viral rebound. Incomplete virologic response to therapy is defined for all children with any of the following: A less than 1.0 decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA of greater than 400 copies/μL after 6 months of therapy.

Breastfeeding

In the United States and other parts of the world where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, breastfeeding by HIV-infected women (including those receiving antiretroviral drugs) is not recommended.[73]

Observational data and randomized clinical trials have demonstrated that infant prophylaxis (primarily using daily infant nevirapine) during breastfeeding significantly decreases the risk of postnatal transmission in breast milk and that maternal triple-drug prophylaxis during breastfeeding may likewise decrease postnatal infection. The results from a randomized, double-blind, placebo-controlled trial confirm that nevirapine prophylaxis via breastfeeding infants up to age 6 months provides protection from transmission of HIV-1 from mother to child.[74]

Both infant nevirapine prophylaxis and maternal triple-drug prophylaxis during breastfeeding may be associated with the development of antiretroviral drug resistance in infants who become infected despite prophylaxis.

Drug interactions with anti retroviral drugs

Antiretroviral drug (ARD) regimens often contain 3 or more agents. In addition, other drugs are typically required to manage the numerous infectious and systemic consequences of AIDS.

Therefore, the likelihood of drug interactions increases. The outcome of the drug interactions may reduce or eliminate the efficacy or increase the toxicity of 1 or both drugs. A thorough understanding of the mechanisms of interactions is essential to minimize or prevent adverse effects and to prevent inadequate treatment.

Regarding the mechanisms, drug interactions are classified as pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions alter drug absorption, distribution, or elimination (metabolism, excretion). Pharmacodynamic alterations manifest as additive, synergistic, or antagonistic drug effects.[75]

Several ARDs may affect or be affected by absorption kinetics. Didanosine contains an aluminum and magnesium buffer that may affect the absorption of other drugs (eg, ciprofloxacin). Delavirdine, atazanavir, and rilpivirine are poorly absorbed when the pH of the GI tract increases.

Prophylaxis and Treatment of Opportunistic Infections:

Although current HAART regimens have substantially and dramatically decreased AIDS-related OIs and deaths, prevention and management of OIs remain critical components of care for HIV-infected children.[76]

OIs are typically an indication of severe immune suppression. However, an increased capacity to mount inflammatory reactions as a result of successful HAART may result in the development of immune reconstitution inflammatory syndrome (IRIS), which manifests as worsening of an existing active, latent, or occult OI. Although IRIS has primarily been reported in adults after initiation of HAART, it also has been reported in children .

IRIS may unmask viable pathogens. Alternatively, in so-called paradoxical IRIS, symptomatic relapse reflects reconstitution of specific T-cell–mediated immunity against persisting antigens from dead organisms; cultures in these cases are sterile.[77]

Hospital Admission:

Based on the patient's living arrangements and stage of infection, inpatient care may be warranted at some time during the patient's illness. The extensive testing required to rule out an underlying infection or a malignancy may be easiest performed if the child is admitted to a health care facility.

If an infection or a malignancy is detected, hospital admission may be appropriate. For example, if intravenous antibiotics are given, a child is usually admitted to the hospital. A serious reaction to an antiviral drug may also mandate hospitalization to follow up on the progression of the reaction and to observe the patient if new drugs are begun.

Diet:

Malnutrition with an accompanying failure to thrive is not uncommon in children infected with HIV. The patient's dietary habits should be reviewed on a regular basis, and a nutritional specialist should be involved in the patient's treatment.[78]

Poor appetite results in poor nutritional intake. Appetite stimulants can be useful.

High-energy, high-protein nutritional supplements are commonly needed. Caretakers must be instructed to avoid giving the child any food or water that has a high risk of being contaminated with any infectious agent. HIV and accompanying opportunistic infections can worsen GI symptoms.

Nasogastric, nasojejunal, and/or gastrostomy tubes may be needed to support the patient's nutritional and fluid status. Gastrostomy tubes are well tolerated, and they are often more comfortable than nasogastric or nasojejunal tubes.[78]

Treatment Compliance:

Medication compliance is a central issue. This is particularly important with regard to ART because missing even 1 dose can easily lead to subtherapeutic levels of many drugs used in ART. Subtherapeutic levels promote the development of drug resistance.

The treatment regimen may be difficult. Patients must take multiple doses of several ARDs every day, as well as prophylactic antibiotics and supplemental vitamins. Therefore, the risk of missing a dose is high. New ARDs are being

developed to simplify the medical regimen. The simplest dosing regimen should be carefully selected to help avoid this pitfall. Noncompliance with prescribed medications is multifactorial and major in some populations. In general, children do not like to take medications, especially if they taste bad. Several drugs have an unpleasant taste.[79] Adverse effects (eg, GI upset, diarrhea, allergy) may cause the caretaker to discontinue a medication without informing the physician. Many drugs can cause compliance problems, even in the most reliable individuals.

The caretaker or child should bring the medications to each clinic visit. The bottles should be checked against a list of prescribed medications kept in the chart.

Deterrence/Prevention:

The risk of vertical transmission may be reduced. Most children are infected by means of vertical transmission. Proper treatment of the mother during pregnancy and delivery and proper treatment of the neonate can reduce the risk of vertical transmission. Prenatal, perinatal, and postnatal treatment along with elective cesarean delivery lower the transmission rate to as low as 2%.

Immunizations:

Immunizations for most childhood diseases and other preventable pathogens should be given to the child with HIV infection. All typical childhood vaccines should be given, with the exception of live vaccines in selected children.

Inactivated poliovirus vaccine should be given instead of the live oral poliovirus vaccine, though this is a consideration only in developing countries where live oral vaccines are used.[80]

The measles-mumps-rubella (MMR) vaccine should be given to all children whose disease is not in CDC immune category 3. The second dose should be given as soon as 1 month after the first dose to ensure early seroconversion. If a recent measles epidemic has occurred, the measles or mono-measles vaccine should be administered as early as possible to all children, except those whose disease is in CDC immune category 3.

Consultations:

An infectious disease specialist usually provides primary care and coordinates the care of the other specialists. In general, assembling a team of specialists is the best approach for managing the medical care of a child with HIV infection. A human development specialist, a nutritionist, a psychologist, and a case manager should be involved in the treatment of every child with HIV infection.[81]

Examinations by specialists should occur routinely. Obtain a neurodevelopmental evaluation every 3-6 months.

The patient should follow up with an ophthalmologist every 6-12 months. Obtain an ophthalmologic evaluation for CMV, tuberculosis, and toxoplasmosis infections, as well as for corneal ulceration, which is often secondary to underlying nutritional deficits. Obtain dental examinations at age 1-2 years, with follow-up every 3-6 months. Obtain an audiologic evaluation at age 2 years or sooner if concern exists. Surgical consultation may be indicated in patients requiring central venous access for long-term parenteral medication or hyperalimentation. Placement of subcutaneous ports is common in children requiring long-term parenteral therapy, but the risks of placing such a line should be weighed against the possible need for recurrent replacement because of repeated line infections.

A cardiologist, endocrinologist, gastroenterologist, nephrologist, neurologist, pulmonologist, and mental health specialist should be consulted when necessary.[82]

Long-Term Monitoring:

Children with HIV infection require regular monitoring, with intervals determined by age and clinical status (eg, every 2 wk initially in infancy, with an increase in intervals as the child ages and the immune status stabilizes). In younger children, evaluations should occur every 1-6 months. In older children, a review of systems is advised every 3 months and a physical evaluation should be performed every year. $CD4^+$ counts must be checked every 3-6 months.

Accurate height and weight documentation at each visit is important because HIV infection is known to adversely affect growth rates in children. Children with improved height growth velocity may be less likely to exhibit virologic or immunologic failure and less likely to have clinical disease progression.[83] A decrease in the growth velocity should alert the clinician to worsening of the underlying disease or inadequate nutrition.

Dietary habits should be reviewed at each clinical visit. Aggressive nutritional management prevents growth failure and improves immune function. Most children with HIV infection have some developmental delay. Developmental assessment and therapy (including physical, occupational, and speech therapies) should be available.

When to Initiate Therapy in Antiretroviral-Naive Children:

- The Panel has updated recommendations for when to initiate therapy in ARV-naive HIV-infected children to incorporate the updated Centers for Disease Control and Prevention (CDC) Surveillance Case Definition for HIV

Infection, which aligns children with adult and adolescent patients. It includes age-specific CD4 values, indicating a preference for the use of CD4 count over CD4 percentage in all ages.

- The Panel has now stratified the urgency for initiation of combination antiretroviral therapy (cART), recommending urgent initiation in all children younger than 12 months and in those aged 12 months and older with CDC Stage 3-defining opportunistic illnesses or Stage 3 CD4 counts. The text provides guidance that in situations requiring urgent initiation of treatment,[84] the clinical team should expedite a discussion on adherence and provide increased, intensive follow-up in the first few weeks to support the children and families.

What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children[85]

- The Panel has added integrase strand transfer inhibitor-based regimens as agents to be used in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs). Raltegravir can be used in children age 2 years and older and dolutegravir in children aged 12 years and older. Raltegravir is also licensed for infants as young as 4 weeks but the Panel would consider usage only in special circumstances.
- The protease inhibitor (PI) atazanavir boosted with ritonavir is now considered an alternative PI in children aged 3 months through 5 years and remains a preferred drug for children 6 years and older.
- The two-NRTI combination of zidovudine and lamivudine or emtricitabine is now considered an alternative combination for adolescents older than 13 years.

Specific Issues in Antiretroviral Therapy for Neonates:

- The Panel has added a new section about ART for neonates to address specific issues raised by the ability to diagnose HIV infection within a few days of birth in conjunction with growing discussion and reports of early intensive ART of HIV-infected infants and infants at high risk of HIV infection.
- Available information about dosing and safety of individual ARV drugs in term and pre-term infants is summarized and discussed in the context of the benefits and risks of early intensive treatment.
- The Panel cautions that existing pharmacokinetic (PK) and safety data are insufficient for the recommendation of a complete combination antiretroviral therapy (cART) regimen to treat preterm infants and term infants younger than 15 days (until 42 weeks postmenstrual age).[86]

- The Panel recommends that neonatal care providers who are considering a three-drug ARV treatment regimen of term infants younger than 2 weeks or premature infants contact a pediatric HIV expert for guidance and individual case assessment of the risk/benefit ratio of treatment and for the latest information on neonatal drug doses.

Management of Medication Toxicity:

Toxicity table sections have been reviewed and updated throughout. Notable changes include newer data on the occurrence and management of central nervous system (CNS) adverse effects of efavirenz and the effects on creatinine determination of newer ARV drugs dolutegravir, cobicistat, and rilpivirine.[87]

Central Nervous System Toxicity: The toxicity table has been updated to reflect recent reports indicating that a greater proportion of patients than previously recognized experience persistent CNS symptoms due to efavirenz and new information about suicidality associated with this drug. Major depression or suicidal thoughts are now specified as psychiatric illnesses warranting cautious use of efavirenz. Explicit recommendation is made to discontinue efavirenz for severe and/or persistent symptoms when a suitable alternative exists.

Nephrotoxic Effects: The toxicity table has been updated to include a section about elevation in serum creatinine with drugs that cause an asymptomatic decrease in renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in glomerular filtration rate: dolutegravir, cobicistat, rilpivirine.[88]

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

- The Panel has added a new bulleted recommendation to emphasize the need to consider past episodes of ARV treatment failure, tolerability, and all prior drug resistance testing results to avoid choosing new ARV drugs for which archived drug resistance would limit activity.

Medication Summary:

Antiretroviral drugs (ARDs) are used for the treatment of human immunodeficiency virus (HIV) infection and for postexposure prophylaxis (PEP). ARD monotherapy does not produce sustained clinical benefits, such as improved survival. This failure is partly due to the development of drug-resistant variants of HIV. Resistance develops rapidly during monotherapy, and cross-resistance among related drugs is common. Combination therapy with ARDs (a strategy analogous to the treatment of TB and other infectious diseases) has improved efficacy, minimized toxicity, and delayed drug resistance.

Six classes of ARDs currently exist, as follows:[70]

- Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Integrase inhibitors (IIs)
- Fusion inhibitors (FIs)
- Chemokine receptor antagonists (CRAs)

Initial therapy should be started with a combination of 3 ARDs, including a backbone of 2 NRTIs plus an NNRTI or a protease inhibitor.

◆ **Nucleoside Analogue Reverse Transcriptase Inhibitors**

- **Zidovudine:** The panel has updated the dosing table to include the dose for continuation of zidovudine after 4 or more weeks based on gestational age.

◆ **Non-Nucleoside Analogue Reverse Transcriptase Inhibitors**

- **Nevirapine:** The Panel has provided information about the investigational treatment dose of nevirapine for infants younger than 1 month with a link to the new section, Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants.
- **Rilpivirine:** The panel has updated dosing for adolescents and adults to include switching to rilpivirine in appropriate virologcially-suppressed patients.[89]

◆ **Protease Inhibitors**

- **Atazanavir:** June 2014, the FDA approved the powder formulation of atazanavir for infants and children 3 months and older who weigh at least 10 kg but less than 25 kg. The Panel provides information about dosing and administration of atazanavir powder and discusses issues related to transitioning from atazanavir powder to capsules. Because there is no FDA approved atazanavir powder dose for the child who reaches a weight of 25 kg and cannot swallow pills, the Panel has provided information about an experimental dose currently under study for children who weigh 25 to < 35kg. Information is also provided about the use of cobicistat tablets for boosting atazanavir in adolescents 18 years and older and adults. Information has also been added about administration and dosing of atazanavir with cobicistat in adolescents and adults.

- **Darunavir:** Information has been added about administration and dosing of darunavir with cobicistat in adolescents 18 years and older and adults.

◆ **Integrase Strand Transfer Inhibitors**

- **Dolutegravir:** The Panel has provided information about the investigational dose being used in a clinical trial for treatment-experienced children younger than 12 years.[90]
- **Elvitegravir:** A tablet formulation of elvitegravir was FDA approved in September 2014 for adults; it is not approved for children younger than 18 years. The Panel has provided dosing recommendations for the use of elvitegravir in combination with other ARV drugs.

◆ **Pharmacokinetic Enhancers**

- **Cobicistat:** A new section has been added because cobicistat is now available as a tablet and in combination with atazanavir (Evotaz) or darunavir (Prezcobix) as well as the previously available Stribild (emtricitabine-tenofovir disoproxil fumarate-elvitegravir-cobicistat). Cobicistat is notinterchangeable with ritonavir. See dosing information for specific PI and elvitegravir that require cobicistat for boosting.
- **Ritonavir:** Information about ritonavir has been moved because it is used as a PK enhancer of other PI in children and adults and is no longer recommended as an antiviral agent. In adults, ritonavir is recommended as a PK enhancer for use with the integrase inhibitor elvitegravir, when used in combination with another PI.[91]

The Global Plan for Elimination of Pediatric HIV:

In 2011, Ambassador Eric Goosby of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and Michel Sidibe, Executive Director of Joint United Nations Programme on HIV and AIDS (UNAIDS), formally announced a plan for eliminating new HIV infections in children and keeping their mothers alive. The elimination of pediatric HIV agenda, or the Global Plan, calls for decreasing new pediatric infections by 90% and halving maternal deaths from HIV and AIDS by 2015 [92]. This newest call to action strengthens previous global commitments to reduce the number of vertical HIV infections with concomitant decreases in mortality from HIV and AIDS and mortality in children under age 5. While high-level rhetoric is necessary to mobilize resources, the strategy to end mother-to-child transmission of HIV (eMTCT) has thus far focused primarily on the expansion of prevention of mother-to-child transmission (PMTCT) with little attention focused on infected children or those missed by current programming. This strategy places at risk a whole

generation of children who despite our best efforts are missed by current PMTCT programming and continue to become infected with HIV. Eliminating MTCT is a worthy aspiration, and while the 2015 goal is ambitious, we are closing the gap. Expanding the focus on pediatric HIV is a collective effort and many experts in the field are aligned on what they know to be the existing barriers and potential solutions to ensuring equity in access to care and treatment for children infected and affected by HIV. The evolution of the WHO treatment guidelines is a case in point. The 2010 WHO PMTCT guidelines called for earlier initiation and extended periods of prophylaxis in pregnant and breastfeeding women to ensure protection throughout the duration of potential HIV exposure. Consensus has since emerged that earlier introduction of antiretroviral therapy (ART) in pregnant women is safer than imagined and results in lowered viral load and decreased vertical transmission [93]. The 2013 WHO guidelines will move us closer to a "test and treat" paradigm by expanding recommendations for lifelong ART for all pregnant and lactating women, which is routine practice in developed countries where vertical transmission is now seen as a rare but tragic curiosity.

Challenges in Eliminating Pediatric AIDS

The goal of eliminating pediatric AIDS will elude us, however, if we continue to rely solely on PMTCT scale-up. In the 2 years since the announcement of the Global Plan, the number of new infections has decreased by only 38% from 2009 levels in the 21 priority countries where 90% of HIV-positive pregnant women reside [94]. Challenges that remain in these countries include low antenatal clinic attendance and retention in care, suboptimal adherence to therapy, and non-existent case finding measures to identify HIV-infected children. Eliminating pediatric AIDS requires developing and expanding strategies to reach children missed by current programming. We know that early treatment for HIV-positive children offers their best hope for survival [95], and we have the ability to diagnose and deliver such treatment. Despite impressive scale-up of PMTCT programming in high-burden countries such as Botswana and Namibia, and the implementation of Option B+ in Malawi, Uganda, and elsewhere, vertical transmission and pediatric HIV infection remain significant challenges throughout the world. Countries such as the Democratic Republic of Congo and Nigeria are falling behind efforts to eliminate new infections and contribute nearly half of the global burden of new pediatric infections. In 2012, 210,000 new pediatric infections were added to the pool of 3.4 million children infected with HIV worldwide, and while data from 2012 are not yet available, in 2011, 230,000 children died from AIDS-related illnesses [96].

Patient Education: Educating parents regarding the importance of compliance with prescribed medications and health care visits is a major challenge because of many factors. See Deterrence/Prevention for further discussion about this topic. Patients should be educated regarding the transmission of HIV. Increasing their awareness of the mechanism and consequences of HIV transmission is important. Safe social interactions that do not expose people to an increased risk for HIV transmission should also be emphasized.[97]

When was the St. Jude HIV program started and what does it offer:

In 1987, St. Jude founder Danny Thomas declared AIDS a catastrophic disease of children. It was then that HIV/AIDS became a research priority of St. Jude. Since that time, the St. Jude Department of Infectious Diseases has developed a broad, multidisciplinary pediatric program called the Pediatric AIDS Clinical Trials Unit (PACTU), which has been designated a "Center of Excellence" by the Robert Wood Johnson Foundation. The St. Jude HIV program for children and youth includes the following:[98,99]

- **A broad, dedicated team**: The staff consists of doctors, nurse practitioners, nurses, social workers, pharmacists, a psychiatrist, a psychologist, a chaplain and a Child Life specialist. All of these people specialize in pediatric and youth-specific issues.
- **Continuity of HIV care**:

  HIV-infected patients from birth through 21 years of age are accepted in the program and are provided the latest, recommended HIV care. Patients are supported through 24 years of age and then transition to an adult care provider of the patient's choice. A health care provider can refer an HIV-infected child or youth to St. Jude using one of the contact methods listed on the patient referral website.
- **A respected research program**:

  The St. Jude HIV program is a well-recognized research center and takes part in numerous National Institutes of Health (NIH) and pharmaceutical industry studies. Supported by the NIH, St. Jude is a site for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), the Adolescent Trials Network (ATN) and the Pediatric HIV/AIDS Cohort Study (PHACS).
- **Clinical trials**: Through clinical trials, patients in the St. Jude HIV program have access to cutting-edge research including new drugs in development.

- **A commitment to the community**: The St. Jude HIV clinical staff is committed to the cause of HIV education and prevention in the community. Our doctors, nurse practitioners and social workers provide HIV education and prevention presentations throughout the community and local school system.

Conclusion

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported, new antiretroviral (ARV) drugs are approved, and new approaches to treatment are recommended. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional ARV drugs become approved and optimal strategies for use of these drugs in children becomes better understood, the Panel will modify these guidelines. These guidelines are only a starting point for medical decision-making and are not meant to supersede the judgment of clinicians experienced in the care of HIV-infected children. Because of the complexity of caring for HIV-infected children, and the decreasing number of children with perinatally acquired HIV in the United States, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist.

The Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics jointly developed and published guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children.

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