



Pediatric AIDS

Overview

The National Institute of Allergy and Infectious Diseases (NIAID) has a lead role in research devoted to children infected with the human immunodeficiency virus (HIV), the virus that causes the acquired immunodeficiency syndrome (AIDS).

NIAID-supported researchers are developing and refining treatments to prolong the survival and improve the quality of life of HIV-infected infants, children and adolescents. Many promising therapies are being tested in the Pediatric AIDS Clinical Trials Group (ACTG), a nationwide clinical trials network jointly sponsored by NIAID and the National Institute of Child Health and Human Development (NICHD). Scientists also are improving tests for diagnosing HIV infection in infants soon after birth so that therapy can begin as soon as possible.

Epidemiologic studies are examining risk factors for transmission as well as the course of HIV disease in pregnant women and their babies in an era of antiretroviral therapy. Researchers have helped illuminate the mechanisms of HIV transmission as well as the distinct features of pediatric HIV infection and how the course of disease and the usefulness of therapies can differ in children and adults.

Researchers also are studying ways to prevent transmission of HIV from mother to infant. Notably, Pediatric ACTG investigators have demonstrated that a specific regimen of zidovudine (AZT) treatment, given to an HIV-infected woman during pregnancy and to her baby after birth, can reduce maternal transmission of HIV by two-thirds. Many consider this finding to be one of the most significant research advances to date in the fight against HIV and AIDS.

The Scope of the Problem

UNAIDS and the World Health Organization (WHO) estimate that by late 1996, 2.6 million children worldwide had been infected with HIV and 1.3 million had died as a result. By 2000, the WHO projects that 5 to 10 million children will have been infected with HIV, with another 5 to 10 million children orphaned by the HIV/AIDS pandemic.

In the United States, through December 1996, 7,629 cases of AIDS in children younger than 13 and 2,754 cases in those aged 13 through 19 had been reported to the Centers for Disease Control and Prevention (CDC). Many other children are currently infected with HIV but have not yet developed AIDS.

HIV infection ranks seventh among the leading causes of death for U.S. children 1 to 14 years of age. In many cities in the northeastern United States, HIV disease is the leading cause of death among children ages 2 to 5.

Transmission

Almost all HIV-infected children acquire the virus from their mothers before or during birth, a process called *perinatal transmission*. In the United States, approximately 25 percent of pregnant HIV-infected women not receiving AZT therapy have passed on the virus to their babies.

Most perinatal transmission, causing an estimated 50 to 80 percent of infections in children, probably occurs late in pregnancy or during birth. Although the precise mechanisms are unknown, scientists think HIV may be transmitted when maternal blood enters the fetal circulation, or by mucosal exposure to virus during labor and delivery. The role of the placenta in maternal-fetal transmission is unclear and the focus of ongoing research.

The risk of perinatal transmission is significantly increased if the mother has advanced HIV disease, increased levels of HIV in her bloodstream, or fewer numbers of the immune system cells -- CD4+ T cells -- that are the main targets of HIV.

Other factors that may increase the risk of perinatal transmission are maternal drug use, severe inflammation of fetal membranes, or a prolonged period between membrane rupture and delivery. A recent study sponsored by NIAID and others found that HIV-infected women who gave birth more than four hours after the rupture of the fetal membranes were nearly twice as likely to transmit HIV to their infants, as compared to women who delivered within four hours of membrane rupture.

HIV also may be transmitted from a nursing mother to her infant. Recent studies suggest that breast-feeding introduces an additional risk of HIV transmission of approximately 14 percent among women with chronic HIV infection. The WHO recommends that all HIV-infected women be advised as to both the risks and benefits of breast-feeding of their infants so that they can make informed decisions. In countries where safe alternatives to breast-feeding are readily available and economically feasible, this alternative should be encouraged. In general,

in developing countries where safe alternatives to breast-feeding are not readily available, the benefits of breast-feeding in terms of decreased illness and death due to other infectious diseases greatly outweigh the potential risk of HIV transmission.

Prior to 1985 when screening of the nation's blood supply for HIV began, some children were infected through transfusions with blood or blood products contaminated with HIV. A small number of children also have been infected through sexual or physical abuse by HIV-infected adults.

Preventing Perinatal HIV Transmission

In 1994, a landmark study conducted by the Pediatric ACTG demonstrated that AZT, given to HIV-infected women who had very little or no prior antiretroviral therapy and CD4+ T cell counts above 200/mm³, reduced the risk of maternal-infant transmission by two-thirds, from 25 percent to 8 percent.

In the study, known as ACTG 076, AZT therapy was initiated in the second or third trimester and continued during labor, and infants were treated for six weeks following birth. AZT produced no serious side effects in mothers or infants; long-term follow-up of the infants and mothers is ongoing.

Researchers have subsequently shown that this AZT regimen has reduced perinatal transmission in other populations in which it has been used. Several recent observational studies in the United States and Europe indicate that similar reductions in perinatal HIV transmission can be achieved by using this regimen in regular clinical care settings.

Following up on the success of ACTG 076, the Pediatric ACTG has begun new perinatal HIV prevention trials that build on the AZT regimen. These trials include additional antiretrovirals in an attempt to reduce perinatal HIV transmission even more than that achieved by AZT alone.

The AZT regimen used in ACTG 076 is not always available because of cost and logistical demands. Therefore, NIAID is pursuing a global strategy that assesses whether simpler and less costly regimens for preventing mother-to-infant HIV transmission can be effective in various settings.

Because a significant amount of perinatal HIV transmission occurs around the time of birth, and the risk of maternal-fetal transmission depends, in part, on the amount of HIV in the mother's blood, it may be possible to reduce transmission using drug therapy only around the time of birth.

NIAID has planned other studies that will assess the effectiveness of

this approach as well as the role of new antiretrovirals, microbicides and other innovative strategies in reducing the risk of perinatal transmission.

Diagnosis

HIV infection is often difficult to diagnose in very young children. Infected babies, especially in the first few months of life, often appear normal and may exhibit no telltale signs that would allow a definitive diagnosis of HIV infection. Moreover, all children born to infected mothers have antibodies to HIV, made by the mother's immune system, that cross the placenta to the baby's bloodstream before birth and persist for up to 18 months. Because these maternal antibodies reflect the mother's but not the infant's infection status, the test is not useful in newborns or young infants.

In the past few years, investigators have demonstrated the utility of highly accurate blood tests in diagnosing HIV infection in children 6 months of age and younger. One laboratory technique called polymerase chain reaction (PCR) can detect minute quantities of the virus in an infant's blood. Another procedure allows physicians to culture a sample of an infant's blood and test it for the presence of HIV.

Currently, PCR assays or HIV culture techniques can identify at birth about one-third of infants who are truly HIV-infected. With these techniques, approximately 90 percent of HIV-infected infants are identifiable by 2 months of age, and 95 percent by 3 months of age. One innovative new approach to both RNA and DNA PCR testing uses dried blood spot specimens, which should make it much simpler to gather and store specimens in field settings.

Progression of HIV Disease in Children

Researchers have observed two general patterns of illness in HIV-infected children. About 20 percent of children develop serious disease in the first year of life; most of these children die by age 4 years.

The remaining 80 percent of infected children have a slower rate of disease progression, many not developing the most serious symptoms of AIDS until school entry or even adolescence.

A recent report from a large European registry of HIV-infected children indicated that half of the children with perinatally acquired HIV disease were alive at age 9. Another study, of 42 perinatally HIV-infected children who survived beyond 9 years of age, found about one-quarter of the children to be asymptomatic with relatively intact immune systems.

The factors responsible for the wide variation observed in the rate of disease progression in HIV-infected children are a major focus of the

NIAID pediatric AIDS research effort. The Women and Infants Transmission Study, a multisite perinatal HIV study funded by NIH, has found that maternal factors including Vitamin A level and CD4 counts during pregnancy, as well as infant viral load and CD4 counts in the first several months of life, can help identify those infants at risk for rapid disease progression who may benefit from early aggressive therapy.

Signs and Symptoms of Pediatric HIV Disease

Many children with HIV infection do not gain weight or grow normally. HIV-infected children frequently are slow to reach important milestones in motor skills and mental development such as crawling, walking and speaking. As the disease progresses, many children develop neurologic problems such as difficulty walking, poor school performance, seizures, mental retardation and cerebral palsy.

Like adults with HIV infection, children with HIV develop life-threatening opportunistic infections (OIs), although the incidence of various OIs differs in adults and children. For example, toxoplasmosis is seen less frequently in HIV-infected children than in HIV-infected adults, while serious bacterial infections occur more commonly in children than in adults. Also, as children with HIV become sicker, they may suffer from chronic diarrhea due to opportunistic pathogens.

Pneumocystis carinii pneumonia (PCP) is the leading cause of death in HIV-infected children with AIDS. PCP, as well as cytomegalovirus (CMV) disease, usually are new infections in children, whereas in adults these diseases result from the reactivation of latent infections.

A lung disease called lymphocytic interstitial pneumonitis (LIP), rarely seen in adults, also occurs frequently in HIV-infected children. This condition, like PCP, can make breathing progressively more difficult and often results in hospitalization.

Children with HIV suffer the usual childhood bacterial infections -- only more frequently and more severely than uninfected children. These bacterial infections can cause seizures, fever, pneumonia, recurrent colds, diarrhea, dehydration and other problems that often result in extended hospital stays and nutritional problems.

HIV-infected children frequently have severe candidiasis, a yeast infection that can cause unrelenting diaper rash and infections in the mouth and throat that make eating difficult.

Treatment of HIV-Infected Children

Anti-HIV Therapies. NIAID investigators are defining the best treatments for pediatric patients. Largely due to studies in the Pediatric ACTG, four anti-HIV agents are currently approved for use in children. In addition, two protease inhibitors are now approved for children with HIV disease.

Most doctors consider giving anti-HIV therapy to children who have HIV-related symptoms or who have laboratory evidence of immunosuppression.

NIAID-supported researchers have demonstrated that two treatment regimens -- ddI alone or in combination with AZT -- are each superior to AZT alone in children who have had little or no previous antiretroviral therapy. Many other promising new antiretroviral regimens are being assessed for use in children in the Pediatric ACTG, including various combinations of nevirapine, d4T, lamivudine (3TC), and 1592U89. The Institute also is undertaking clinical trials of new protease inhibitors in pediatric patients, as well as novel treatment approaches such as gene therapy. The overall trend in both adult and pediatric HIV disease management is for early and aggressive use of combination antiretroviral therapy to keep HIV virus replication at as low a level as possible.

Opportunistic Infections. Many medications used to treat adults with opportunistic infections are effective in children when given in appropriate doses. For example, 85 percent of HIV-infected children are able to tolerate trimethoprim-sulfamethoxazole (TMP/SMX) for PCP. This drug is extremely effective in preventing new or recurrent PCP in children and is the first choice for pediatric patients, as it is in adult patients. NIAID studies are assessing alternative treatments to prevent PCP in children who do not benefit from or cannot tolerate TMP/SMX.

NIAID investigators are developing pediatric formulations of other agents commonly used against OIs, and to understand how children absorb and metabolize these drugs.

Immune Product Studies. Clinical trials sponsored by NIAID and NICHD have demonstrated that intravenous immunoglobulin (IVIG), a preparation containing many types of antibodies, can reduce bacterial infections frequent in children with AIDS. However, the NIAID study suggested that the benefits of IVIG are confined to those patients who had not received TMP/SMX as preventive therapy for PCP. Studies are now underway to assess whether specially made immune globulin products with extra antibodies to HIV can further improve the health status of children with HIV.

AIDS in Adolescents

Adolescents account for a rapidly growing percentage of the reported AIDS cases in the United States. Although less than 1 percent of AIDS patients in the United States are between 13 and 19 years of age, this figure underestimates the significance of HIV transmission during adolescence.

Since the average period of time from HIV infection to the development

of AIDS is 10 years, the majority of people in their twenties with AIDS were likely infected as adolescents. Approximately 20 percent of all reported cases of AIDS in the United States have occurred in young adults between the ages of 20 and 29.

Several recent studies have found that increasing numbers of teenagers are becoming infected with HIV, especially in poor, urban areas as well as in rural areas of the South. Surveys of military recruits and Job Corps participants as well as blinded seroprevalence studies indicate that as many as one in 20 individuals aged 15 to 20 years from certain populations in the northeastern and southern United States are HIV-infected.

Psychosocial Issues

A disproportionate number of children with AIDS belong to minority groups: 84 percent of children reported with AIDS in 1996 in the United States were black or Hispanic. Most live in inner cities, where poverty, illicit drug use, poor housing and limited access to and use of medical care and social services add to the challenges of HIV disease. A mother and child with HIV usually are not the only family members with the disease. Often, the mother's sexual partner is infected, and other children in the family may be infected as well. Frequently, a mother with AIDS does not survive to care for her HIV-infected child.

Management of the complex medical and social problems of families affected by HIV requires a multidisciplinary case management team, integrating medical, social, mental health and educational services. NIAID provides special funding to many of its clinical research sites to provide for services, such as transportation, day care, and the expertise of social workers, crucial to families devastated by HIV.

Resources

AIDS Clinical Trials Information Service. For information about pediatric and adult AIDS clinical trials open to enrollment, call (800) TRIALS-A, 9 a.m. to 7 p.m. Eastern Time, Monday through Friday. World Wide Web address: <http://www.actis.org>

National AIDS Hotline. Staffed 24 hours a day, seven days a week. (800) 342-AIDS.

The National Pediatric HIV Resource Center. (800) 362-0071.

The Pediatric AIDS Foundation. (415) 883-1796.

The Pediatric Branch of the National Cancer Institute conducts clinical trials for HIV-infected children on the NIH campus in Bethesda, Md. (301) 402-0696.

NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies and immunology.

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