Journal of Developmental and Physical Disabilities, Vol. 8, No. 3, 1996

Pediatric HIV Infection: A Review of Epidemiology, Clinical Manifestations, and Current Intervention

Deborah A. Pearson,[1,4] Marilyn D. Doyle,[2] Larry K. Pickering,[3] and Juliana Ortegon[1]

Human Immunodeficiency Virus (HIV) infection has emerged as a global epidemic that is predicted to kill many thousands of children by the end of this century. In this review, several aspects of pediatric HIV infection are presented. The epidemiology of HIV infection is briefly surveyed in the United States, Africa, Europe, the Caribbean, and Asia. Clinical manifestations of pediatric HIV infection, which are not entirely congruent with the signs and symptoms often found in adults, are also reviewed, including medical, neurological, developmental, and behavioral manifestations of this disease process. Finally, an intervention program outlining current medical, pharmacological, and neurodevelopmental follow-up care is discussed.

KEY WORDS: HIV infection; pediatrics; neurodevelopment; epidemiology; antiretroviral treatment.

INTRODUCTION

From the time it was first described in the United States in the early 1980's, human immunodeficiency virus (HIV) infection has been a central public health issue. This disease has reached epidemic proportions (Oleske, 1990a) and remains incurable. HIV infection produces immune deficien-

[1]Department of Psychiatry and Behavioral Sciences, University of Texas Medical School at Houston, Houston, Texas 77030.
[2]Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas 77030.
[3]Center for Pediatric Research, Eastern Virginia Medical School, Norfolk, Virginia 23510.
[4]To whom correspondence should be addressed.

1056-263X/96/0900-0179$09.50/0

cies, and the resulting Acquired Immune Deficiency Syndrome (AIDS) is characterized by a wide variety of opportunistic infections and malignancies. The term AIDS is used to describe the stage of the disease process that meets the Centers for Disease Control, CDC, or the World Health Organization, WHO, criteria for AIDS (i.e., symptomatic illness). The term HIV infection refers to both symptomatic or asymptomatic illness that does not meet the AIDS defining criteria. Although first described in homosexual men, HIV infection has spread to other segments of society, including individuals with hemophilia, heterosexual men and women, intravenous (IV) drug abusers, and infants born to infected mothers (Ianetti *et al.*, 1989). In 1993, approximately 7000 infants were born to women with HIV infection in the United States (CDC, 1995b).

EPIDEMIOLOGY OF PEDIATRIC HIV INFECTION

United States

AIDS has become and will probably continue to be one of the largest causes of death in American children from any single infectious disease agent (Chin, 1994). In 1991, HIV/AIDS was the seventh leading cause of death for children between the ages of 1 and 4 years and the ninth leading cause of death for children between 5 and 14 years of age (Willoughby, 1994). Approximately 1.5% of all reported AIDS cases in the United States occur in children; as of June 1994, the CDC had received reports of 5734 cases of AIDS among children less than 13 years of age (CDC, 1994b). It is estimated that 10,000 children are currently infected with HIV (NIAID, 1994) and that approximately 1000 to 2000 infants are infected annually (CDC, 1995b; Chin, 1994; Gwinn *et al.*, 1991). These figures foreshadow the future numbers of infants and children who are likely to develop AIDS.

Most children diagnosed with either HIV or AIDS are younger than 5 years old (CDC, 1994a), reflecting the fact that in 1994, 91.7% of infants and children with AIDS were infected through vertical transmission of HIV (CDC, 1995a). This statistic represents children who were infected with HIV from an infected mother during pregnancy (i.e., gestationally), during the perinatal period (50% of vertical HIV infection is thought to occur at this time; Luzuriaga *et al.*, 1993), or postnatally from breastfeeding. While it is difficult to separate the risk of HIV infection attributable to breastfeeding from other confounding maternal risk factors, at least ten case reports of apparent vertical transmission of HIV via breastfeeding have been reported (Ziegler *et al.*, 1984; Lederman, 1992).

In addition to vertical transmission, other vectors of pediatric HIV have been identified. Prior to the advent of improved blood donor screening and heat inactivation of blood products in 1984, contaminated clotting factor was a major risk factor for transmission of HIV for individuals with hemophilia (Hilgartner *et al.*, 1993). At this point, approximately 57 percent of children with hemophilia in the United States are HIV seropositive as a result of contaminated blood products (Hilgartner *et al.*, 1993). In actual numbers, Gomperts (1990a, b) estimates that there are at least 2400 HIV-infected children with hemophilia nationwide. CDC data from 1993 indicate that two percent of the pediatric AIDS cases reported that year are a result of hemophilia and/or a coagulation disorder (CDC, 1994a). Another 3% of reported pediatric AIDS cases are believed to have resulted from receipt of a blood transfusion, blood components, or tissue (CDC, 1994a).

The mode of transmission for 2% of the pediatric cases in 1993 is unknown or not reported (CDC, 1994a). Although there are reports of transmission of HIV through child sexual abuse, the incidence of HIV infection through this mode of transmission is unknown (Gellert *et al.*, 1990; Gutman *et al.*, 1991; Oleske, 1990b). With at least 250,000 to 300,000 cases of sexual abuse reported in the United States each year (Krugman, 1986; Sarafino, 1979) and the increasing prevalence of HIV infection, this method of HIV transmission is likely to be a growing problem among the pediatric population.

In the majority of the pediatric AIDS cases in which the virus is passed from the mother to the child, the mother's infection is linked to her own or to her sexual partner's use of IV drugs (CDC, 1995b). Heterosexual contact, however, is the most rapidly increasing route of HIV transmission for women (CDC, 1995b). Pediatric AIDS affects minority groups disproportionately. In 1993, approximately 55% of the cumulative pediatric AIDS cases were found in African American children, 25% in Hispanic children, and 20% in Caucasian children (CDC, 1994a).

Although the major method of spread of pediatric AIDS is by vertical transmission of HIV from the mother to the infant, not all infants born to HIV-infected mothers will contract HIV infection. The Working Group on Mother-to-Child Transmission of HIV (1992) reports transmission rates of 13 to 32% in industrialized countries. Another study estimates that the transmission rate in the United States is 25 to 30% (Krywanio & Fisher, 1992). It should be noted, however, that rate of vertical transmission may decrease considerably in the future, given that it has recently been determined that a regimen of prenatal, perinatal, and postnatal zidovudine has been associated with a 67% reduction in rate of transmission (Connor *et al.*, 1994).

Diagnosis of HIV infection in the newborn infant is problematic. All infected mothers carry antibody to the virus, which is passed to the fetus through the placenta. As a result, all newborn infants of HIV-infected mothers test positive for HIV using antibody-based tests such as the ELISA and Western blot tests, which result in false positive for infants who are not infected with the virus itself. Children who are not infected become antibody-negative by the ELISA and Western blots tests when the maternal antibodies break down (a process that can take up to 18 months, AAP, 1994); these children are referred to as "seroreverters." Newer diagnostic techniques, such as polymerase chain reaction (PCR), viral culture, or acid-dissociated p24 antigen assays have allowed a definitive diagnosis of at least 50% of newborns, with 95% being correctly diagnosed by 3 months of age (Ammann, 1994; Consensus Workshop, 1992; Miles *et al.*, 1993).

For children who are truly infected, age of onset of AIDS defining symptomatology varies. The limited data available suggest that the majority of children infected perinatally have shorter latency periods than those infected by transfusion as neonates (Eyster, 1991). For children under age 13 who have transfusion-acquired infection, analysis of CDC AIDS surveillance data (Eyster, 1991) suggests that the median time for HIV infection to development of AIDS is 41 months. This rate of progression to AIDS is faster than that observed in adults infected through transfusion, which has been estimated by Eyster (1991) to range from 4.5 years to 18 years.

In contrast to transfusion-acquired HIV, evidence suggests that the majority of vertically infected infants presents with symptoms in the first year of life (APA, 1989; Scott *et al.*, 1989). However, it should be noted that a small proportion of vertically infected children remain asymptomatic beyond 7 years of age (Krasinski *et al.*, 1989).

International

The pediatric AIDS epidemic is not limited to the United States. Indeed, the World Health Organization (WHO) estimates that there are currently 1.5 million cases of pediatric HIV infection throughout the world, and it is projected that by the year 2000 that there will be 10 million cases of pediatric HIV infection (NIAID, 1994; WHO, 1995). As these figures suggest, many other nations are experiencing far most devastating impacts of pediatric HIV infection than the United States. In developing nations, 5 to 25% of the reported cases of AIDS are in children (NIAID, 1994).

Four areas which have been particularly hard hit include Africa, parts of Europe, the Caribbean, and Asia.

Africa

African countries in which the reported prevalence of AIDS cases (combined pediatric and adult) are in excess of 10,000 are Uganda, United Republic of Tanzania, Zimbabwe, Malawi, Kenya, Zambia, Zaire, Cote d'Ivoire, Ethiopia, Ghana, Rwanda (WHO, 1995). As a result of the fact that in some regions of sub-Saharan Africa, more than 20% of women of reproductive age are HIV positive (Datta *et al.*, 1994), it is felt that the percentage of AIDS cases among children is far greater in Africa (~15-20% of total AIDS cases; Ruff *et al.*, 1990) than it is in the United States (~1.5%; CDC, 1994b). Chin (1994) projects that by the year 2000, there will be 2.5 million infants infected with HIV, with 1.7 million cases of pediatric AIDS in sub-Saharan Africa. These figures are also associated with high mortality rates. In a recent prospective study conducted in Kinshasa, Zaire, children with vertically acquired HIV infection experienced a 3-year mortality rate of 44%, compared to the 6% rate in children with HIV-seronegative mothers (Ryder *et al.*, 1994). Although most cases of HIV infection are currently found in the cities of Africa, in the next decade, it is expected that the rate of HIV in rural areas will exceed the city rates—largely due to the fact that Africa is overwhelmingly rural (Grant, 1989).

Pediatric AIDS is acquired primarily through vertical transmission (Morgan *et al.*, 1990; Muller *et al.*, 1990; Piot and Tezzo, 1990); such rate of transmission has been estimated to be as high as 25–50% (Hira *et al.*, 1989; Lepage *et al.*, 1991; Ryder *et al.*, 1994). Breastfeeding also contributes to the vertical transmission rate. Datta *et al.* (1994) report that children who were breast-fed for 15 months or longer were at substantially increased risk of infection. Medical injections and use of unsterile instruments are not major modes of transmission (Muller *et al.*, 1990); however, blood transfusions have been an important risk factor in the spread of HIV infections (Lepage and Van de Perre, 1988). Due to difficulties in screening all blood donations, blood transfusions continue to represent a significant risk of HIV transmission for at least some regions of Africa (Shaffer *et al.*, 1990; Ryder, 1992). Unfortunately, even after children with HIV infection are identified, antiretroviral treatments, which could prolong life and improve the quality of life, are often unavailable to children due to weak distribution networks, inadequate clinical facilities, and lack of financial support (Preble, 1990).

Europe

The prevalence of AIDS in Europe is similar to that of the United States. Many more men than women have been diagnosed as having AIDS, and approximately 2% of all AIDS cases occur among children (Peckham and Newell, 1990). Newell (as cited in Francis, 1994) reported that by the end of September 1992, 3577 children with AIDS had been reported within Europe and that mother-to-child transmission accounted for approximately 80% of pediatric HIV infection. The largest numbers (≥10,000 cases) of cases (pediatric and adult) of AIDS in Europe are reported in France, Spain, Italy, and Germany (WHO, 1995). In particular, given its population, Romania appears to have been especially devastated by pediatric HIV infection due to a lack of disposable needles and medical supplies, and with a policy of transfusing untested blood (Patrascu, Constantinescu, and Dublanchet, 1990; Rudin *et al.*, 1990; Ruff *et al.*, 1990; WHO, 1995).

Rate of vertical transmission in Europe is currently estimated to be approximately 15% (European Collaborative Study, 1994). Diagnosis is typically made shortly after birth, the median age of presentation of symptoms being 8 months (European Collaborative Study, 1991). Results from a natural-history study of vertically infected children suggest that about 25% of infected children develop AIDS in the first year of life and about 40% by the age of four (European Collaborative Study, 1994). Following diagnosis, treatment is far more accessible to European infants, as compared with African infants (Peckham and Newell, 1990).

Caribbean

Pediatric AIDS is a significant issue in the Caribbean, given that 9% of total AIDS cases are pediatric (CAREC, 1990). Although these countries are very small in comparison to African and European nations, there are more than 1000 cases (combined pediatric and adult) in Haiti, Trinidad and Tobago, and the Bahamas (WHO, 1995). Using a demographic projection model for the English-speaking Caribbean countries, one study estimates that around the year 2000, 12% of the AIDS cases will be in the pediatric population (Newton *et al.*, 1994). The patterns of HIV transmission are also similar to Africa. Like Africa, HIV infection is spreading rapidly to rural areas from the cities, and where the primary mode of transmission is through heterosexual contact, with similar infection rates in men and women (Schill *et al.*, 1989).

Asia

Currently, Asia is home to the fastest growing HIV epidemic (Berkley, 1993). The spread of HIV is particularly noteworthy in South and Southeast Asia with recent estimates suggesting that 2 million persons may be infected and that the number of new infections will surpass that in Africa before the end of the decade (Chin, 1994; Berkley, 1993). Chin (1994) projects that by the year 2000, there will be 440,000 infants infected with HIV, with 300,000 cases of pediatric AIDS in Southeast Asia. As with the United States, HIV infection initially appeared among male homosexuals and intravenous drug users, but heterosexual transmission quickly became the most common mode of transmission (Smith, 1990; Weller, 1994; Berkley, 1993). However, unlike the United States, contaminated blood products are still believed to represent a significant vector for HIV transmission in some Asian countries (Weller, 1994).

CLINICAL MANIFESTATIONS OF PEDIATRIC HIV INFECTION

The clinical manifestations of pediatric HIV infection differ significantly from the pattern typically seen in adults with HIV infection. The Center for Disease Control (CDC) has devised a separate classification scheme for children which takes these differences into account. Young infants typically present with failure to thrive (FTT), developmental delay, and neurological impairment. As indicated in Table I, other manifestations include generalized adenopathy, chronic diarrhea, lymphadenopathy chronic parotiditis, and lymphoid interstitial pneumonitis, a pulmonary process occurring in 30% to 50% of infected children but rarely seen in adults (Bobat *et al.*, 1990; Pizzo *et al.*, 1988). Frequently, children with HIV infection also have recurrent serious bacterial infections such as pneumonia, sepsis, and meningitis (Oleske, *et al.*, 1983; Oleske, 1990a; Pizzo *et al.*, 1988a). With early recognition, these infections are usually amenable to standard therapies. In the later stages of disease, children are afflicted with the more unusual opportunistic pathogens such as *Pneumocystitis carinii*, oropharyngeal thrush [which can lead to a number of vocal and feeding problems (Pressman, 1992)], *Mycobacterium avium-intracellularae*, cytomegalovirus, other viral and fungal organisms. HIV infection has also been linked to the development of malignancies; however, these malignancies are less commonly seen in children than in adults (Pizzo *et al.*, 1988a).

Table I. Manifestations of Pediatric HIV Infection

A. Medical manifestations
1. Failure to thrive
2. Chronic diarrhea
3. Lymphadenopathy
4. Chronic parotitis
5. Lymphoid interstitial pneumonitis
6. Bacterial infections
   a. Pneumonia
   b. Sepsis
   c. Meningitis
7. Pneumocysitis carini
8. Oropharyngeal thrush
9. Mycobacterium avium-intracellulare
10. Cytomegalovirus

B. Neurological manifestations
1. Encephalopathy
2. Acquired microencephaly
3. Ventricular dilatation
4. Calcification of the basal ganglia

C. Developmental manifestations
1. Motor delays
   a. Loss of milestones
   b. Plateauing of milestones
2. Cognitive delays
   a. Speed of information processing
   b. Attention
   c. Verbal and nonverbal memory
   d. Language
   e. Academic achievement

D. Behavioral/psychological manifestations
1. Adaptive behavior delays/losses
2. Irritability
3. Apathy
4. Hyperactivity
5. Anxiety
6. Depression

Neurological Manifestations of Pediatric HIV Infection

From the early 1980s, it was strongly suspected that HIV affected the nervous system because many patients demonstrated signs of dementia as the disease process progressed. It was later confirmed that HIV was neurotropic (Falloon *et al.*, 1989; Price *et al.*, 1988); evidence of HIV has been found in the brain and in the cerebrospinal fluid (CSF), and its presence in the CSF was correlated with the clinical occurrence of neurological deterioration (Belman, 1994; Epstein *et al.*, 1988). Infection can occur at very early stages of fetal development (Belman, 1994). The

best documented neurological complication of AIDS is encephalopathy, which is a manifestation of degeneration of brain tissue (Belman *et al.*, 1986; Belman, 1990b; Ultmann *et al.*, 1985). This encephalopathy can be progressive, with degeneration continuing during the course of the disease, or it can be static, where the degeneration reaches a certain point and then plateaus (Belman *et al.*, 1985; Belman, 1990; Elder and Sever, 1988, Shaw *et al.*, 1985). Associated with the encephalopathy is a characteristic acquired (i.e., secondary) microcephaly, in which the head circumference is typically within normal limits at birth but becomes progressively smaller as cortical atrophy progresses (Belman *et al.*, 1985; Ultmann *et al.*, 1985). Such encephalopathy is associated with a number of developmental delays and deterioration, as outlined below. As the cortical atrophy progresses, changes also occur in the ventricles. The ventricles become larger as the brain tissue surrounding them atrophies, producing a characteristic prominence of these CSF spaces, as seen in CT scans of children with AIDS (Barnes, 1986; Belman *et al.*, 1985; Olofsson, 1989). Ventricular dilatation and cortical atrophy have long been associated with cognitive problems in other groups of children with developmental disabilities such as premature infants (Weisglas-Kuperus *et al.*, 1987; Williamson *et al.*, 1982).

Other neurological problems have been associated with HIV infection in children. One widely documented problem is calcification of the basal ganglia (Belman, 1994; Belman *et al.*, 1986; Epstein *et al.*, 1986; Ultmann *et al.*, 1985), which are structures in the extrapyramidal system of the brain associated with motor function. Damage to these structures is associated with involuntary motor movements and problems with muscle tone. Indeed, a variety of fine and gross motor disorders has been documented in children with AIDS, including rigidity, dystonic posturing, tremor, awkward gait, and refusal to walk (Belman, 1990a, b; Coulter *et al.*, 1988; Diamond *et al.*, 1990; Epstein *et al.*, 1988a; Price *et al.*, 1988).

Belman (1990a, 1994) reported that even facial expressions are affected. The children acquire an alert, wide-eyed expression, but have a paucity of spontaneous facial movements. There is also restriction of eye movements, particularly in the upward gaze, reduced eye blink, and abnormal pursuit. Other disease related factors thought to be associated with movement disorders in these children include lymphomas, hemorrhages, CNS infection (Belman, 1900b; Ianetti *et al.*, 1989), and vacuolar myelopathy, which is degeneration of the material responsible for the conducing of nerve impulses (Navia *et al.*, 1986; Petito, 1988). At end-stage, a child with AIDS may become quadriparetic (Belman, 1990a).

Developmental Manifestations of Pediatric HIV Infection

A number of developmental declines are closely associated with the neurological deterioration caused by HIV infection in children. In fact, it was the developmental deterioration in these children that originally pointed to neurological deficits (Ultmann *et al.*, 1985). Subsequent research has directly linked the developmental course of the infant and child with AIDS to the degree of encephalopathy (Belman, 1990b; Chamberlain, 1993; Diamond *et al.*, 1990). While it is important to remember that other factors, such as prematurity, prenatal exposure to toxic substances (such as alcohol and other drugs), and poor nutrition may also affect development in these children (Ultmann, 1985, 1987), certain patterns of development have been linked to HIV infection, even when these factors are similar in HIV+ and HIV-comparison groups (e.g., Aylward *et al.*, 1992).

While almost all infants born to HIV infected mothers are initially seropositive, a substantial number of these infants will serorevert within the first 15 months. Unlike the true seropositive infants, these seroreverters have a developmental course that is not significantly different than infants who are seronegative from birth (Aylward *et al.*, 1992; Hittelman, 1990; Msellati, 1993). Although the developmental status of the true seropositives is not distinguishable from that of the seroreverters at birth, or even at 3 months, by 6 months the true seropositives have a significantly higher rate of developmental disability than do seroreverters (Hittelman, 1990). Thus, although routinely available blood tests do not definitely distinguish true seropositives from seropositives who will serorevert until the age of 15 months, the developmental status of the infant can substantially distinguish the two groups by as early as 6 months. As previously noted, new laboratory tests, such as a viral culture from blood and polymerase chain reaction (PCR), have helped in establishing an earlier diagnosis of HIV infection in this age group.

As Aylward *et al.* (1992) have noted, the developmental status of the children with HIV (i.e., the seropositives) offers insight into other aspects of HIV. Lack of developmental differences between infants who were HIV- from birth and infants who become HIV- after birth (i.e., the seroreverters) suggests that in utero exposure to HIV does not result in infant cognitive or motor delays. Furthermore, the fact that HIV+ infants exhibit more delays than seroreverters suggests that these delays are not the result of parental overprotectiveness or increased medical involvement, because the medical intervention for all of these subgroups was identical, as was presumably parental attention (at least prior to discovering the non-infected status of the seroreverters).

A prominent developmental pattern seen in these infants and children is motor delay. These delays occur in both fine and gross motor skills. The pattern of deterioration can be a failure to acquire new motor skills or a loss of previously acquired milestones (Belman, 1990b; Epstein *et al.*, 1988b; Hittelman, 1990; Olofsson, 1989). Most of these children have a progressive motor dysfunction, which is related to the child's developmental status at the time of CNS infection. In the infant, motor dysfunction may be expressed as hypotonia (decreased muscle tone), while in an older child, such dysfunction might be expressed as a change in gait or refusal to walk. Motor dysfunctions are especially crucial during the period of infancy, because it is through the child's ability to operate on his or her environment that cognitive gains are made (Piaget and Inhelder, 1969). Coulter *et al.* (1988) have related the inability of HIV infected infants to reach or to use midline skills to deficits in these infants' exploration of their environment, which in turn result in cognitive delays.

Cognitive delays are another central characteristic associated with HIV-infection (Belman, 1990b; Hittelman, 1990; Loveland and Stehbens, 1990; Ultmann, 1985). Hittelman (1990) reported that 36% of her sample of HIV-infected children had IQs assessed to be within the range of mental retardation, whereas by definition, only 2% of the general population is thought to have an IQ in this range of functioning. Similarly, Price *et al.* (1988) and Msellati *et al.* (1993) found evidence of significant levels of neurodevelopmental delays or abnormalities in their samples. However, Cohen *et al.* (1991) did not find significant differences between HIV+ and HIV- children on global intellectual ability, even 4-1/2 to 8-1/2 years after infection. A similar pattern has been found by Loveland et al. (1994) and Whitt *et al.* (1993), who noted similar neuropsychological profiles in HIV+ hemophiliacs, as compared to HIV- hemophiliacs. Thus, infants and children with HIV infection have sometimes, but not always, been found to have deficits in global intellectual functioning.

In addition to these global estimates of functioning, research has suggested that there may be more specific areas of functioning that are associated with declines. The speed of information processing in general has been found to be slower in children who are HIV+ (Loveland and Stehbens, 1990), their ability to be attentive is also compromised by their disease (Coutler *et al.*, 1988; Hittelman, 1990; Loveland and Stehbens, 1990), as are their verbal (and in some cases, nonverbal) memory skills (Loveland and Stehbens, 1990). Cohen *et al.* (1991) found evidence of deficits on tasks assessing visual scanning, academic achievement, cognitive flexibility, and motor speed in children who were HIV+. These experimental findings corroborate the subjective impressions reported by these

patients of their being mentally slow, unable to concentrate, and forgetful (Barnes 1986; Krener and Miller, 1989).

Another area in which deficits have been commonly reported is that of language development (Belman, 1990b; Ultmann *et al.*, 1985). Hittelman (1990) reported that 27% of the children in her HIV infected sample were language delayed. Young children may use fewer gestures as time goes on, while older children vocalize less. These disturbances in language are often progressive, and in the endstage of the disease, the child may become mute (Belman, 1990b). Interestingly, although language skills are delayed in these children, they are commensurate with the child's overall cognitive status (Ultmann *et al.*, 1985). Language ability is strongly related to academic performance, and these children show declines in academic achievement, especially in the area of mathematics (Loveland and Stehbens, 1990).

Although a definite pattern of developmental delays or deficits is associated with HIV infection, a few points should be noted. For instance, most medically asymptomatic children with HIV are indistinguishable from their noninfected peers on a variety of neurological and psychological indices (e.g., Cohen *et al.*, 1991; Loveland *et al.*, 1994; Sirois and Hill, 1993). Sirois and Hill (1993) suggested that children infected at older ages (e.g., by transfusion) may manifest fewer delays in some areas (e.g., visual motor development) than those infected at younger ages. They point out that even in areas in which HIV+ children showed weaker performance than their uninfected peers, their performance was within normal limits for their age. However, when children who were HIV+ but indistinguishable from their uninfected peers were tracked over time, they eventually developed subtle declines in some facets of verbal and perceptual abilities (Sirois and Hill, 1993).

Although developmental delays have been well-documented in children with HIV infection, the pattern of developmental decline has been found to take one of several courses. Belman (1990b, 1994) has outlined three patterns of decline: the "plateau," the "plateau followed by deterioration," and the "plateau followed by improvement." In the "plateau," infants and young children gain few new developmental milestones, or do so at a very slow rate; however, they do not lose previously acquired milestones. Thus, developmental status of these infants and children remains at approximately the same level over long periods of time. In the "plateau followed by deterioration" pattern, the child maintains a plateau for a period of time but then begins to lose developmental milestones (Belman *et al.*, 1988). In the final pattern, "plateau followed by improvement," the child begins to acquire new skills after a long period of plateau. This pattern is not common, and all of Belman's patients eventually relapsed. These

different patterns of developmental decline have been linked with progressive encephalopathy, static encephalopathy, and reversals in encephalopathy due to drug (zidovudine or ZDV, aka "AZT") intervention (Brouwers *et al.*, 1990; Epstein *et al.*, 1988b; Pizzo *et al.*, 1988b). It should be noted that even children whose absolute level of developmental status remains on a plateau are really declining relative to their peers, because their peers continue to make developmental gains over time while these children do not. As Loveland and Stehbens (1990) point out, this is especially true in infancy, which should be a period of exponential growth in cognitive skills. An HIV-infected infant who is plateauing during this period is actually showing precipitous declines from the normal pattern of tremendous growth during this period.

Behavioral/Psychological Manifestations of Pediatric HIV Infection

In addition to declines in developmental functioning, evidence has accumulated documenting the decline in behavioral adjustment in these children. Unfortunately, as Armstrong *et al.* (1993) note, much less is known about psychopathology in children with HIV than is known about their developmental and cognitive problems. Hittelman (1990) and Loveland and Stehbens (1990) have found significant declines in adaptive functioning, or practical living skills (e.g., social behavior, personal care, range of activities). It has been noted that these children become progressively more irritable and lose interest in their environment. They may also become inattentive, hyperactive, and develop conduct problems at school and at home (Levenson and Mellins, 1992; Lifschitz *et al.*, 1989). They may also become indecisive and apathetic (Belman, 1990b; Loveland and Stehbens 1990; Perry, 1990; Levenson and Mellins, 1992). In adults, serious problems with stress, anxiety, and depression, and a variety of organic mental disorders, have long been associated with HIV infection (Hassan and Douglas, 1990). This mental status has been linked to suicide. Marzuk *et al.* (1988) found that the suicide rate in HIV-infected men age 29–59 was *66* times greater than the suicide rate in the general population, and Krener and Miller (1989) note that up to 80% of persons who are HIV+ have had suicidal ideation. Hassan and Douglas (1990) feel that mental status may impact health status through biochemical means. They suggest that stress reactions may lead to altered release patterns of neurohormones and/or neuropeptides, which in turn may affect the progression of the disease.

When considering psychological adjustment to illness, developmental status must be taken into account because the manner in which psycho-

logical conflict is expressed differs in children who are in different stages of cognitive development (Lapham and Shevlin, 1986; Waters *et al.*, 1988). While younger children may choose more concrete methods of expressing conflict in response to chronic illness, such as acting out, or refusing to eat, older children typically express these conflicts through more abstract means, such as anxiety or depression (Pearson and Pumariega, 1991).

In addition to the individual psychological adjustment problems experienced by the child, there are broader family issues to consider. Problems encountered by any family dealing with a chronic illness include lack of resources, social isolation, prejudice, boredom, and depression (Oloffson, 1989; Waters *et al.*, 1988). Treatment for the illness imposes a variety of other problems, including hospitalizations, separation, effects of treatment regimens, and the undermining of family support mechanisms. These factors frequently result in feelings of anger and helplessness, which unfortunately can be expressed as a family's refusal to administer medications or to keep medical appointments (Mangos *et al.*, 1990). As Brantley *et al.* (1981) point out, families that are many times initially dysfunctional wind up in utter chaos when confronted by chronic illness. Such stressors are reflected in the living situations of children with HIV infection: in one study, only 20-25% of these children lived in the home of their biological family, while the majority lived in foster care (Hopkins, 1989).

The aforementioned problems are magnified in the case of families facing HIV-related illness, given the tremendous stigmatization associated with this disease. These families face issues related to confidentiality, loss of housing, termination of employment, loss of access to medical care when insurance coverage is discontinued, and death of family members (Seibert *et al.*, 1989). Furthermore, they face the issues noted while also enduring the financial impact of HIV disease, estimated several years ago to range from $3500 (for health care costs alone) for an asymptomatic child with HIV to over $50,000 per year for a severely symptomatic child (Mangos *et al.*, 1989). As the Ryan White case illustrated, children with AIDS may suffer from the vehement reactions of parents of other children when these parents find that a child with HIV will be attending school with their child (Liss and Younkin, 1987). Interestingly, Walker and Hulecki (1989) found that this attitude is not reflected in the attitudes of special education teachers: AIDS was not found to be a biasing factor in teachers' judgments about special education services. Unfortunately, this was not the case in the child day care setting where significant biases by parents of children in day care and by care providers were found to exist against HIV-infected children (Morrow *et al.*, 1991). As it can be reasonably hypothesized that the psychosocial conflicts experienced by the child and his family, both at home and in the community, may directly impact the functional status of the

the child, these factors must also be addressed in any type of intervention program.

In summary, children with HIV infection are at high risk for a number of developmental problems. These difficulties include a variety of medical problems, with neurological deficits figuring prominently into the pattern associated with the progression of the disease. Neurological deficits are associated with a variety of developmental delays, which in turn impact the degree of academic and behavioral adjustment for the child. As with any chronic illness, such children and their families are also at high risk for the development of serious psychosocial conflicts and family decay. Of course, access to intervention is often compromised by a number of cultural and language barriers for many of these families (Mangos *et al.*, 1990).

INTERVENTION

Given the multifaceted manifestations of HIV illness in children, intervention for this illness must incorporate a number of different approaches. These treatment strategies include medical, pharmacological, and neurodevelopmental care and follow-up. The following is a description of the interdepartmental program to are for children with HIV infection that has been developed at the University of Texas Medical School in Houston.

Medical Intervention

Pediatric Human Immunodeficiency Virus infection is the newest chronic illness of childhood. While HIV disease is clearly a fatal illness, progression to death is often a prolonged process. The goal in treating HIV infected infants and children is to maintain normal growth, development, and health for as long as is possible and to assist the child to maximize his or her potential to the greatest degree possible.

The most critical factor in insuring effective medical care for HIV infected children is to provide comprehensive care wherein the child's medical, social, and psychosocial needs are met. This goal requires a team approach to the child and family. Team members optimally include pediatricians, obstetricians, nurses, social workers, and psychologists.

In the ideal situation, medical intervention is initiated prior to the birth of the child. This approach allows the team to establish rapport with the family, review prognosis for the infant, educate the family about HIV disease, discuss available resources, and introduce research protocols that are available. Since the most common mode of transmission of pediatric

HIV disease is perinatal, all mothers of infected infants are also infected, mandating the need for clinical care in these women. In an attempt to simplify the maze of medical care these families face, a joint clinic for infants and mothers in the same clinical setting ideally is established at the same time of day. This arrangement not only simplifies care for the families but also permits immediate interaction among physicians to occur.

All infants born to HIV infected women should be followed during the first 2 years of life, during which HIV infection can be established or ruled out. By providing primary care it is possible to continuously educate the families about HIV infection and prevention of further spread, to intervene and assist family members when difficult situations arise, and to avert crises that could negatively impact on the child's health.

Preventive medical care should also be provided. The HIV-infected children (and often siblings) should receive childhood immunizations in the HIV clinic. The health of the infected children and their parents may depend on the fact that other family members are immune to common infections, such as measles and influenza, which can have devastating consequences for the immunosuppressed members of the family. HIV infected children receive all recommended childhood immunizations, including measles, mumps, and rubella vaccines. It is recommended, however, that they and their household contacts be given inactivated polio vaccine. The nutritional status of children should be continuously assessed, and the parents should be educated about routine child care including nutrition, growth and development, discipline, and safety issues.

The children should be carefully monitored for evidence of HIV infection both clinically and through laboratory studies. The common early clinical signs of HIV infection are persistent thrush, failure to thrive, and developmental delay. Infants should have blood obtained for an HIV culture or polymerize chain reaction (PCR) within the first 3 months of life. A positive culture, or two positive PCR's, is diagnostic of infection. In addition, the absolute CD4 positive T-lymphocyte count and CD4 (helper cells)/CD8 (cytotoxic/suppressor cells) ratio should be monitored since a low CD4 count and abnormal CD4/CD8 ratio have been shown to be predictive of infection as early as 6 months of age (Prover and Gershon, 1991). Elevation of serum immunoglobins, especially IgA, is also indicative of infection.

Most importantly, the child needs to have an identified medical provider who not only oversees primary care but also is available to manage intercurrent illnesses and exacerbations of HIV symptoms. This approach assures that families have rapid access to medical care when children become ill. When children are treated for intercurrent illness in a timely fashion, many complications can be prevented and the need for lengthy

hospitalization can often be averted. In addition, the primary medical provider can coordinate the child's treatment by interacting with the various subspecialists who inevitably become involved in the child's care. It is the responsibility of the primary medical care provider to make the final treatment decisions, in conjunction with the family. When the child becomes terminal, the primary provider can provide support for the difficult decisions that families must make at this time.

Pharmacological Intervention

Pharmacological intervention in children with HIV infection involves three areas: (1) prophylaxis for *Pneumocystis carinii* pneumonia (PCP), and bacteria including *Streptococcus pneumoniae*, and *Hemophilus influenza* type b; (2) antiretroviral therapy; and (3) therapy of many other opportunistic infections acquired by HIV-infected children. *Pneumocystis carinii* pneumonia is the most common and lethal opportunistic infection seen in infants and children with HIV infection (CDC, 1991). Incidence of this opportunistic infection is decreased by the prophylactic administration of antimicrobial agents effective against this organism (CDC, 1991). Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra) is the first drug of choice for prophylaxis. The dose is 75 mg/m^2 of trimethoprim twice a day, three times a week. Alternative therapies for children who cannot tolerate TMP-SMZ include monthly aerosolized pentamidine for younger children, and dapsone which has been proven to be an efficacious prophylactic agent in adults (CDC, 1991).

In adults, antimicrobial prophylaxis is initiated when the CD4 count is less than 200 cells/μL. Because the children normally have CD4 counts that are higher than adults, prophylaxis is initiated as follows (CDC, 1991):

<1500 cells/μL for children 1–11 months
<750 cells/μL for children 12–23 months
<500 cells/μL for children 24 months–5 years
<200 cells/μL for children 6 years of age or older

One of the common manifestations of pediatric HIV disease is recurrent bacterial infections, such as pneumonia, bacteremia, sinusitis, and otitis media caused by common agents such as *Streptococcus pneumoniae* and *Hemophilus influenza*. A recently completed clinical trial randomized children with HIV infection to receive placebo or monthly infusions of intravenous gamma globulin (IVIG). This study demonstrated that for children with CD4 counts of 200 cells/μL or greater, monthly infusions of IVIG significantly decreased the number of serious bacterial infections, especially pneumonia and

bacteremia due to *Streptococcus pneumoniae* (National Institute of Child Health and Human Development, 1990). Many clinicians have incorporated the use of monthly IVIG in the treatment of their patients.

Zidovudine or ZDV, and dideoxyinosine (DDI) are the only antiretroviral agents approved for the treatment of HIV infection in both adults and children. Both drugs interfere with the replication of HIV by inhibiting the enzyme reverse transcriptase, which is essential for the production of proviral DNA. The major toxicity of zidovudine is bone marrow suppression. in adults, therapy is initiated when the CD4 count falls to 500 cells/μL. There is no scientific evidence upon which to base the decision to initiate antiretroviral therapy in pediatric patients, however, the following recommendations have been made (HIV Resource Center Workshop on Tetrovial Therapy, 1992):

Age (in years)	CD4 Count	% CD4
<1 year	<1750	<30%
1–2 years	<1000	<25%
2–6 years	<750	<20%
>6 years	<500	<20%

Although an exhaustive review of the effectiveness of antiretroviral therapy is beyond the scope of this presentation, a number of studies have suggested that these drugs may improve neuropsychological functioning. Pizzo *et al.* (1988b) found that 6 months of continuous-infusion ZDV treatment of infants and children was associated with clinically significant developmental gains, and Brouwers *et al.* (1990) noted that these gains were maintained after 12 months. Wolters *et al.* (1994) noted similar gains in adaptive behavior, or everyday living skills, with ZDV treatment. DeCarli *et al.* (1991) found that these developmental gains were accompanied by demonstrative reduction in encephalopathy, as measured by computed tomography (CT) scans. A very exciting development in the field of antiretroviral treatment of HIV was noted by the AIDS Clinical Trial Group (ACTG) Protocol 076, which demonstrated a significant reduction in vertical transmission of HIV from 25.5% to 8.3% with prenatal (after the third month) and perinatal ZDV treatment for HIV+ mothers, followed by 6 weeks of postnatal ZDV treatment for the newborn (Connor *et al.*, 1994).

Unfortunately, as Ammann (1994) notes, viral resistance to ZDV was observed within a few years of its adoption as a treatment agent. Recent preliminary analyses of data generated from the ACTG Protocol 152 has suggested that ZDV was not as effective in treating pediatric HIV (and had higher rates of side effects) than either ddI or ddI in combination with

ZDV (Public Health Service/NIH News Release, 2/13/95). Furthermore, it should be noted that some investigators (e.g., Nozyce *et al.*, 1994) have found no improvement in symptomatology with oral ZDV treatment in vertically infected infants, while Pizzo *et al.* (1990) noted no improvement with dideoxycytidine (ddC) treatment.

Thus, although antiretroviral therapy has been associated with cognitive and behavioral improvements in some situations, as Nozyce (1994) points out, other factors, including socioeconomic status, developmental level at onset of illness, health status at the start of treatment, and treatment administration/compliance issues all directly impact the effectiveness of this therapy. As such, these factors need to be more fully explored in studying medication treatment effects.

Neurodevelopmental Intervention

Because infants and children infected with HIV are at high risk for a number of developmental and academic problems, these problems must be identified and addressed in order for children to reach their full potential. With the advent of improved treatment regimens, children with HIV infection are living longer and this trend can be expected to continue. As such, there will be a growing need for long-term educational planning for them. As with any developmentally disabled individual, this intervention must begin at birth, provide for the proper infant programs, continue through early childhood programs, and then provide transition into regular or special education elementary school programs (Council for Exceptional Children, 1986).

Aside from meeting the academic needs of the identified patient, another important consideration is meeting the psychological needs of the child and his or her family. Failure to meet these needs may directly impact on the course of the illness, or even on morbidity. In addition to assessing the psychological status of the child, it is appropriate to assess the functional status of other family members, particularly other noninfected children in the family. These children are often overlooked during the crisis of the illness, and they will be the ones who survive their infected parents and siblings. Needs of these children must be identified, and they should be provided with ongoing support (Klindworth *et al.*, 1989).

The first step in neurodevelopmental intervention is assessment. The infant or child's neurodevelopmental status is assessed in a number of functional areas, including cognitive, motor, adaptive, and behavioral domains. Development is monitored over time to determine if a child is developing a specific deficit. As noted above, specific developmental deficits are often

associated with neurological deterioration, and these assessments often signal when closer medical scrutiny might be necessary. In our center, we have found that families are most compliant with the neurodevelopmental testing when it is coordinated with medical intervention, since many of these families live at a considerable distance from the center, and repeated trips to the medical center are not feasible.

Infants who are born to HIV positive mothers should be assessed shortly after birth, usually prior to their discharge from the hospital. During this assessment, parents should be counseled about patterns of development of infants with HIV infection, and the importance of follow-up care. If any referrals are indicated, they should be arranged. These follow-up services would include infant stimulation programs, occupational therapy, and physical therapy.

Following the initial assessment, infants should be followed every 3 months until they are 12 months old and every 6 months until they are 3 years old. Although it is possible to perform these assessments in the hospital or the pediatrician's office, it is desirable to perform these evaluations away from the location in which the infant (child) has experienced painful medical procedures. It is a general impression that infants are more relaxed if tested on "neutral" territory such as a child development clinic. Repeated assessments are necessary to closely monitor the progress of the infants during this period of rapid development. Unlike older individuals, it is not anticipated that serious test-retest practice effects would occur from three month testing intervals with infants under 12 months old.

Children over 3 years of age should be tested or screened every 6–12 months. Examples of tests that can be used to assess these older children are listed below. There are many other batteries, including the battery used in the Hemophilia Growth and Development Study (Hilgarter *et al.*, 1993) that are equally effective in monitoring a child's developmental progress. The tests selected for this battery are not meant to represent an exhaustive neuropsychological battery: rather, they were selected because they are psychometrically sound (Fletcher *et al.*, 1991) and are capable of assessing the domains which are most commonly associated with declines with HIV infection. These tests also have been selected for their ease and efficiency of administration since many of these infected children and their mothers have little endurance. It is felt that a battery that is four or 5 h long is too exhausting. The battery optimally should be contained within one testing session, rather than having the family return for testing on several occasions. Some of the scales recommended are parent questionnaires that can be completed at home and returned to the clinic. These scales provide considerable information about a number of behavioral problems; they also provide cursory information about developmental status.

Neurodevelopmental Assessment Procedures

A. Birth

1. *Neonatal Behavioral Assessment Scale* (Brazelton, 1984). The NBAS measures infant development during the neonatal period (birth-28 days). Developmental status is assessed in terms of the infant's orientation and habituation abilities, motor maturity, reflex capabilities, and ability to regulate arousal states.

B. Neonatal Period to 42 Months

1. *Bayley Scales of Infant Development, 2nd Edition* (Bayley, 1993). The Bayley scales measure mental and motor development in infants 16 days to 42 months of age. The test provides a Mental Developmental Index (MDI) which measures visual-motor skills and language development, and a Psychomotor Developmental Index (PDI) which measures both gross and fine motor skills. The most recent version of the Bayley features an extensively redone Behavior Rating Scale, which was formerly called the Infant Behavior Record (IBR).

2. *Minnesota Child Development Inventory* (Colligan, 1977). The Minnesota is a parent questionnaire assessing gross motor, fine motor, language, and adaptive skills in infants and children 6 months to 6-1/2 years old. This measure is useful for screening when an infant (or pre-school child) is unavailable for regular testing (i.e., he or she lives to far away, or is too weak to complete a test battery).

C. Child Assessment Procedures

1. *Stanford-Binet Intelligence Scale (Fourth Edition)* (Thorndike, Hagen, and Sattler, 1986). This fourth revision of the Stanford-Binet scale provides a global estimate of intelligence, together with subscale measures of verbal reasoning, abstract/visual reasoning, quantitative reasoning, and short-term memory. It is normed for individuals 2–23 years old.

2. *Peabody Developmental Motor Scales* (Folio and Fewell, 1983). The Peabody scales assesses gross and fine motor skills, including reflexes, balance, propulsion, hand use, eye-hand coordination and finger dexterity. It is normed for infants and children from birth to 83 months.

3. *Wide Range Achievement Test (3rd Edition)* (Wilkinson, 1993). The WRAT3 measures academic achievement in the areas of spelling, arithmetic, and reading for individuals ages 5 to 74 years old. It is a screening device for academic achievement: deficits detected on this instrument are followed up at school by a more in-depth psychoeducational assessment before a firm diagnosis of a specific learning disability is made.

4. *Vineland Adaptive Behavior Scales (Interview Edition).* The Vineland scale (Sparrow *et al.*, 1984) measures adaptive behavior in four domains: communication, socialization, daily living, and motor (for children under 6 years old). It is administered by interviewing the primary caregiver, and is normed for infants to adults.

5. *Personality Inventory for Children (PIC-R).* The PIC-R (Wirt *et al.*, 1984) is a multidimensional behavioral rating sale for children ages 3-18 years old which is completed by a parent. It is a multidimensional measure of child behavior, affect, and developmental status. Particular strengths of the PIC-R is that it provides information about informant style, and yields several subscales tapping cognitive development.

6. *Child Behavior Checklist (CBCL).* The CBCL (Achenbach, 1991a, 1992) is another multidimensional behavioral rating scale for children ages 2–18 that measures a number of adaptive and internalizing/externalizing behavioral problems, including somatic complaints, anxiety/depression, attention problems, aggression, and social problems. A similar form (the Teacher's Report Form; Achenbach, 1991b), which measures school behavior, is sent to the child's teacher (with parental permission). Particular strengths of the CBCL/TRF include in-depth information regarding social competence/adaptive function, and profiles of overall internalizing/externalizing behavior.

Sibling Assessment Procedures

Given the stressful living situations of families having a child with HIV, the siblings of infants and children with HIV may be neglected or forced to meet unrealistic expectations. As Meyers and Weitzman (1991) note, these patterns often result in resentment, guilt, and loneliness on the part of the siblings. Given this situation, it is also helpful to screen the siblings of the children infected with HIV using the PIC-R or the CBCL for behavioral problems that would endanger their school performance or else further undermine the family's functioning. Although the youth self-report forms of the PIC or the CBCL might provide better insight into the sibling's perception of their functioning, it is often difficult to get these materials returned to the clinic. As such, a parent form of these indices,

completed while the patient is completing neuropsychological testing, is typically used.

Liaison Services

Based upon results of the initial neurodevelopmental assessment, appropriate referrals are made to local agencies. Neurodevelopmental assessments are often able to establish a diagnosis of mental retardation or significant developmental delay; they are also able to identify children requiring more intensive psychoeducational testing to determine if a specific learning disability is present Although some school-age children who are infected with HIV already qualify for Special Education programs by the time they enter our program, many children (especially early in the disease process) have not yet qualified for this designation, although they may be developing specific learning deficits which are typically served by Special Education services. However, given the problems associated with HIV and its treatment regimens, school systems will serve a child with HIV under the "Other Health Impaired" designation. When this situation is suspected, a report of the testing should be sent to the school, along with a request for follow-up testing. Reports of testing should also be sent to infant stimulation programs, early childhood programs, and programs for the hearing and visually impaired when referrals are made to these agencies. Other follow-up services arranged through this program should include physical and occupational therapy, which are prescribed by the referring physician.

School Consultation

Another important liaison activity provided through this program is consultation for school personnel in how to provide for a student with HIV infection. As Meyers and Weitzman (1991) point out, Public Law 94-142 insures access of children with HIV to multidisciplinary education planning. Many teachers and staff are regular classroom teachers, who may not have had the advanced training that special education teachers have for dealing with children who have special needs. This service has been especially effective in providing information for schools in smaller towns which have not had as much experience with children with HIV infection as larger metropolitan areas.

Counseling and Support Services

In children who receive appropriate screening, a variety of developmental, behavioral, and emotional problems can often be identified promptly. Once identified, these children are referred for services including play therapy (for younger children), and traditional psychotherapy (for older children). For children whose expressive and receptive language difficulties preclude traditional verbally mediated intervention, behavior therapy may be an appropriate alternative for specific behavioral problems (Levenson and Mellins, 1992; Speigel and Mayers, 1991). Families should be given the opportunity to participate in a support group providing both education and emotional support. Although many families are reluctant to seek "counseling" services, they are usually willing to talk with someone for "educational" purposes. It is also important for these families to have a mechanism for calling someone when a crisis arises. If an emergency situation develops, the child (or family member) should be immediately referred for crisis intervention and referred for appropriate follow-up care, if necessary. One component of follow-up are that should not be overlooked is temporary respite care, when the family is overwhelmed, or permanent placement in foster care, when there is no immediate family member who can provide ongoing care for the child (Emery *et al.*, 1992).

Finally, previous research within other chronically ill populations (e.g., children with cystic fibrosis or cancer) has suggested that siblings of chronically ill children are also at high risk for developing a variety of behavioral and emotional problems when the family, including the siblings of the ill child, is faced with the stress of dealing with a seriously ill family member (McCollum, 1975). As Sahler and Friedman (1981) note, emotional and behavioral difficulties are often magnified in siblings when their ill sibling dies. The sibling of a child with HIV sometimes faces an even more devastating fate than siblings in other families experiencing chronic illness: sometimes they are the sole survivors of their families. In order to address this issue, the behavioral and emotional adjustment of siblings of the child infected with HIV should be assessed. This assessment enable these problems to be identified early, so that appropriate intervention can be initiated before they seriously compromise the sibling's behavioral adjustment and academic functioning.

In summary, children with HIV infection are at high risk for developing a variety of developmental problems, in addition to the myriad of medical problems associated with this infection. With the advent of improved medical and pharmacological treatment of children with HIV infection, HIV infection is becoming a more chronic manageable illness than it was a decade ago. As a result, these children will live longer and

will be able to benefit from intervention services. The most effective services for these children involve interdisciplinary intervention, including inpatient and outpatient medical facilities, infant programs, school systems, and psychological services. These services may in turn promote the gains in cognitive, motor, and emotional development that may allow each child with HIV infection to reach his or her fullest potential.

ACKNOWLEDGMENTS

The authors would like to dedicate this manuscript to the memories of Marta C. Lifschitz, M.D., and Gale C. Watts, M.A., who worked selflessly for infants and children with HIV, and who are with their "angels" now. Preparation of this article was supported in part by a grant from the Hogg Foundation for Mental Health and by NIH grants AI27551, HB-96040, and M01-RR-02558. We are very grateful for this generous support.

REFERENCES

Achenbach, T. M. (1991a). *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*, University of Vermont Department of Psychiatry, Burlington.

Achenbach, T. M. (1991b). *Manual for the Teacher's Report Form and 1991 Profile*, University of Vermont Department of Psychiatry, Burlington.

Achenbach, T. M. (1992). *Manual for the Child Behavior Checklist/2-3 and 1992 Profile*, University of Vermont Department of Psychiatry, Burlington.

American Academy of Pediatrics (1994). HIV Infection and AIDS. In Peter G. (ed.), *1994 Red Book: Report of the Committee on Infectious Diseases* (23rd edition), American Academy of Pediatrics, 1994, Elk Grove Village, IL, p. 259.

American Psychological Association Task Force on Pediatric AIDS (1989). Pediatric AIDS and Human Immunodeficiency Virus Infection. *Am. Psychologist* 44: 258-264.

Ammann, A. J. (1994). Human immunodeficiency virus infection/AIDS in children: The next decade. *Pediatrics* 93: 930-935.

Armstrong, F. D., Seidel, J. F., Swales, T. P. (1993). Pediatric HIV infection: A neuropsychological and educational challenge. *J. Learn. Dis.* 26: 92-102.

Aylward, E. H., Butz, A. M. Hutton, N., Joyner, M. L., and Vogelhut, J. W. (1992). Cognitive and motor development in infants at risk for human immunodeficiency virus. *Am. J. Dis. Child.* 146: 218-222.

Barnes, D. M. (1986). AIDS-related brain damage unexplained. *Science* 232: 1091-1093.

Bayley, N. (1993). *Bayley Scales of Infant Development: Second Edition*, Psychological Corporation, San Antonio.

Belman, A. L. (1990a). AIDS and pediatric neurology. *Neurologic Clin.* 8: 571-603.

Belman, A. L. (1990b). Neurologic syndromes associated with symptomatic human immunodeficiency virus infection in infants and children. In Kozlowski, P. B., Snider, D. A., Vietze, P. M., and Wisniewski (eds.), *Brain in Pediatric AIDS*, Karger, pp. 45-64.

Belman, A. L. (1994). HIV-1-associated CNS disease in infants and children. In Price, R. W., and Perry, S. W. (eds.), *HIV, AIDS, and the Brain*, Raven Press, Ltd., pp. 289-310.

Belman, A. L., Diamond, G., Dickson, D., Horoupian, D., Llena, J., Lantos, G., and Rubinstein, A. (1988). Pediatric AIDS: Neurological syndrome. *Am. J. Dis. Child.* 142: 29-35.

Belman, A. L., Lantos, G., Horoupian, D., Novick, B. E. Ultmann, M. G. Dickson, D. W., and Rubinstein, A. (1986). AIDS: Calcification of the basal ganglia in infants and children. *Neurology* 36: 1192-1199.

Belman, A. L., Ultmann, M. H., Horoupian, D., Novick, B., Spiro, A. J., Rubinstein, A., Kurtzberg, D., and Cone-Wesson, B. (1985). Neurological complications in infants and children with acquired immune deficiency syndrome. *Ann. Neurol.* 18: 560-566.

Berkley, S. (1993). AIDS in the developing world: A epidemiologic overview. *Clin. Infect. Dis.* 17 (suppl. 2): 329-336.

Bobat, R. A., Coovadia, H. M., and Windsor, I. M. (1990). Some early observations on HIV infection in children at King Edward VIII Hospital, Durban. *South African Med. J.* 78: 524-527.

Brantley, H. T., Stabler, B., and Whitt, J. K. (1981). Program considerations in comprehensive care of chronically ill children. *J. Pediatr. Psychol.* 6: 229-238.

Brazelton, T. B. (1984). *Neonatal Behavioral Assessment Scale*, J. B. Lippincott, Philadelphia.

Brouwers, P., Moss, H., Eddy, J., Balis, F., Poplack, D. G., and Pizzo, P. A. (1990). Effect of continuous-infusion zidovudine therapy on neuropsychologic functioning in children with symptomatic human immunodeficiency virus infection. *J. Pediatr.* 117: 980-985.

CAREC (1990). Epidemiological notes and reports. *West Indian Med. J.* 39: 128-130.

Centers for Disease Control (1991). Guidelines for prophylaxis against Pneumocysti carinii pneumonia for children infected with Human immunodeficiency virus. *Morb. Mortal. Weekly Rep.* 40: No. RR-2, 1-13.

Centers for Disease Control and Prevention (1994a). *HIV/AIDS Surv. Rep.* 5(4): 8-25.

Centers for Disease Control and Prevention (1994b). Recent trends in U.S. AIDS cases reported to CDC. *HIV/AIDS Prev.* 5(2): 4.

Centers for Disease Control and Prevention (1995a). Update: Acquired immunodeficiency syndrome—United States, 1994. *Morb. Mortal. Week. Rep.* 44(4): 64-67.

Centers for Disease Control and Prevention (1995b). Update AIDS among women—United States, 1994. *Morb. Mortal. Weekly Rep.* 44(5): 81-84.

Chamberlain, M. C. (1993). Pediatric AIDS: A longitudinal comparative MRI and CT brain imaging study. *J. Child Neurol.* 8: 175-181.

Chin, J. (1994). The growing impact of the HIV/AIDS pandemic on children born to HIV-infected women. *Clin. Perinatal.* 21(1): 1-14.

Cohen, S. E., Mundy, T., Karassik, B., Lieb, L., Ludwig, D. D., and Ward, J. (1991). Neuropsychological functioning in human immunodeficiency virus type 1 seropositive children infected through neonatal blood transfusions. *Pediatrics* 88: 58-68.

Colligan, R. C. (1977). The Minnesota Child Development Inventory as an aid in the assessment of developmental disability *J. Clin. Psychol.* 33: 162-163.

Connor, E. M., Sperling, R. S., Gelber, R., Kiselev, P., Scott, G., O'Sullivan, M. J., VanDyke, R., Bey, M., Shearer, W., Jacobson, R. L., Jimenez, E., O'Neill, E., Bazin, B., Delfraissy, J., Culnane, M., Coombs, R., Elkins, M., Moye, J., Stratton, P., and Balsley, J. (1994). Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New Engl. J. Med.* 331: 1173-1180.

Consensus workshop. (1992). Maternal factors involved in mother-to-child transmission of HIV-1. *J. Acq. Imm. Def. Synd.* 5: 1019-1029.

Coulter, D. L., Chase, C., and McLean, K. (1988). Possible neuropsychological deficits in infants with Acquired Immunodeficiency Syndrome. *Ann. Neurol.* 24, 358.

Council for Exceptional Children (1986). *Report of the Council for Exceptional Children's Task Force on policy issues relating to the management of students with communicable diseases. A report to the CEC Governmental Relations Committee*, Author, Reston, VA (ERIC Document Reproduction Service NO. Ed 274 138).

Datta, P., Embree, J. E., Kreiss, J. K., Ndinya-Achola, J. O., Braddick, M., Temmerman, M., Nagelkerke, N. J. D., Maitha, G., Holmes, K. K., Piot, P., Pamba, H. O., and Plummer,

F. A. (1994). Mother-to-child transmission of human immunodeficiency virus type 1: Report from the Nairobi study. *J. Infect. Dis.* 170: 1134-1140.

DeCarli, C., Fugate, L., Falloon, J., Eddy, J., Katz, D. A., Friedland, R. P., Rapoport, S. I., Brouwers, R., and Pizzo, P. A. (1991). Brain growth and cognitive improvement in children with human immunodeficiency virus-induced encephalopathy after 6 months of continuous-infusion zidovudine therapy. *J. Acquired Imm. Def. Synd.* 4: 585-592.

Diamond, G. W., Gurdin, P., Wiznia, A. A., Belman, A. L., Rubinstein, A., and Cohen, H. J. (1990). Effects of congenital HIV infection on neurodevelopmental status of babies in foster care. *Devel. Med. Child Neurol.* 32: 999-1105.

Elder, G. A., and Sever, J. L. (1988). AIDS and neurological disorders: An overview. *Ann. Neurol.* 23(suppl): S4-S6.

Emery, L. J., Anderson, G. R., and Annin, J. B. (1992). Child welfare concerns. In Crocker, A. C., Cohen, H. J., and Kastner, T. A. (eds.), *HIV Infection and Developmental Disabilities: A Resource for Service Providers*, Brookes, Baltimore, pp. 95-103.

Epstein, L. G., DiCarlo, F. J., Joshi, V. V., Connor, E. M., Ooeske, J. M., Kay, D., Koenigsberger, M. R., and Sharer, L. R. (1988a). Primary lymphoma of the central nervous system in children with acquired immunodeficiency syndrome. *Pediatrics* 82: 355-363.

Epstein, L. G., Sharer, L. R., and Goudsmit, J. (1988b). Neurological and neuropathological features of human immunodeficiency virus infection in children. *Ann. Neurol.* 23(suppl): S19-S23.

Epstein, L. G., Sharer, L. R., Oleske, J. M., Connor, E. M., Goudsmit, J., Bagdon, L., Robert-Guroff, M., and Koenigsberger, M. R. (1986). Neurologic manifestations of human immunodeficiency virus infection in children. *Pediatrics* 78: 678-687.

European Collaborative Study (1991). Children born to women with HIV-1 infection: Natural history and risk of transmission. *Lancet* 337: 253-260.

European Collaborative Study (1994). Natural history of vertically acquired human immunodeficiency virus-1 infection. *Pediatrics* 94(6): 815-819.

Eyster, M. E. (1991). Transfusion and coagulation factor-acquired human immunodeficiency virus infection. *Pediatr. Infect. Dis. J.* 10: 50-56.

Folio, M. R., and Fewell, R. R. (1983). *Peabody Motor Skills and Activity Cards Manual*, DLM Teaching Resources, Allen, TX.

Falloon, J., Eddy, J., Weiner, L., and Pizzo, P. A. (1989). Human immunodeficiency virus infection in children. *J. Pediatr.* 114: 1-30.

Fletcher, J. M., Francis, D. L., Pequegnat, W., Raudenbush, S. W., Bornstein, M. H., Schmitt, F., Brouwers, P., and Stover, E. (1991). Neurobehavioral outcomes in diseases of childhood. *Am. Psychologist* 46: 1267-1277.

Francis, B. (1994). The incidence of HIV/AIDS in children and their care needs. *Nurs. Times* 90(26): 47-49.

Gellert, G. A., Durfee, M. J., and Berkowitz, C. D. (1990). Developing guidelines for HIV antibody testing among victims of pediatric sexual abuse. *Child Abuse Negl.* 14: 9-17.

Gomperts, E. D. (1990a). Growth and development of HIV-infected hemophiliac children. In Kozłowski, P. B., Snider, D. A., Vietze, P. M., and Wisniewski (eds.), *Brain in Pediatric AIDS*, Basel, Karger, pp. 39-44.

Gomperts, E. D. (1990b). HIV infection in hemophiliac children: Clinical manifestations and therapy. *Am. J. Pediatr. Hematol. Oncol.* 12(4): 497-504.

Grant, J. P. (1989). *UNICEF's Present Policy and New Approaches. The Implications of AIDS for Mothers and Children*, Paris, France. Cited by Ruff *et al.*, 1990.

Gutman, L. T., St. Claire, K. K., Weedy, C., Herman-Giddens, M. E., Lane, B. A., Niemeyer, J. G., and McKinney, Jr., R. E. (1991). Human immunodeficiency virus transmission by child sexual abuse. *Am. J. Dis. Child.* 145: 137-141.

Gwinn, M., Pappaioanou, M., George, J. R., Hannon, W. H., Wasser, S. C., Redus, M. A., Hoff, R., Grady, G. F., Willoughby, A., Novello, A. C., Petersen, L. R., Dondero, Jr., T. J., and Curran, J. W. (1991). Prevalence of HIV infection in childbearing women in the United States: Surveillance using newborn blood samples. *J. Am. Med. Assoc.* 265(13): 1704-1708.

Hassan, N. F., and Douglas, S. D. (1990). Stress-related neuroimmunodulation of monocyte-macrophage functions in HIV-1 infection. *Clin. Immunol. Immunopathol.* 54: 220-227.

Hilgartner, M. W., Donfield, S. M., Willoughy, A., Contant, C. F., Evatt, B. L., Gomperts, E. D., Hoots, W. K., Jason, J., Loveland, K. A., McKinlay, S. M., and Stehbens, J. A. (1993). Hemophilia growth and development study: Design, methods, and entry data. *Am. J. Pediatr. Hemotorl. Oncol.* 15: 208-218.

Hira, S. K., Kamanga, J., Bhat, G. J., Mwale, C., Tembo, G., Luo, N., and Perine, P. L. (1989). Perinatal transmission of HIV-1 in Zambia. *Br. Med. J.* 299: 1250-1252.

Hittelman, J. (1990). Neurodevelopmental aspects of HIV infection. In Kozlowski, P. B., Snider, D. A., Vietze, P. M., and Wisniewski (eds.), *Brain in Pediatric Aids*, Karger, Basel, pp. 64-71.

HIV Resource Center Workshop on Retroviral Therapy (1992). Cited in Johnson, B. (ed.), *Harriet Lane Handbook: A Manual for Pediatric House Officers (13th ed.)*, Mosby, Baltimore, MD, p. 259.

Hopkins, K. M. (1989). Emerging patterns of services and case finding for children with HIV infection. *Ment. Retard.* 27: 219-222.

Ianetti, P., Falconieri, P., and Imperato, C. (1989). Acquired immune deficiency syndrome in childhood: Neurological aspects. *Child's Nerv. Syst.* 5: 281-287.

Klindworth, L. M., Dokecki, P. R., Baumeister, A. A., and Kupstas, R. D. (1989). Pediatric AIDS, developmental disabilities, and education: A review. *AIDS Ed. Prevent.* 1: 291-302.

Krasinski, K., Borkowsky, W., and Holzman, R. S. (1989). Prognosis of human immunodeficiency virus infection children and adolescents *Pediatr. Infect. Dis. J.* 8: 216-220.

Krener, P., and Miller, F. B. (1989). Psychiatric response to HIV spectrum disease in children and adolescents. *J. Am. Acad. Child Adol. Psychiatry*, 28: 596-605.

Krugman, R. D. (1986). Recognition of sexual abuse in children. *Pediatr. Rev.* 8: 25-30.

Krywanio, M. L., and Fisher, D. G. (1992). Meta-analysis of neonatal HIV seroconversion. *Pediatr. AIDS HIV Infect.* 3: 165-169.

Lapham, E. V., and Shevlin, K. M. (1986). *The Impact of Chronic Illness on Psychosocial Stages of Human Development*, Georgetown University and Medical Center, Washington, D. C.

Lederman, S. A. (1992). Estimating infant mortality from human immunodeficiency virus and other causes in breast-feeding and bottle-feeding populations, *Pediatrics* 89: 290-296.

Lepage, P., Dabis, F., Hitimana, D. G., Msellati, P., Van Goethem, C., Stevens, A. M., Nsengumuremyi, F., Bazubagira, A., Serufilira, A., De Clercq, A., and Van de Perre, P. (1991). Perinatal transmissions of HIV-1: Lack of impact of maternal HIV infection on characteristics of livebirths and on neonatal mortality in Kigali, Rwanda. AIDS 5: 295-300.

Lepage, P., and Van de Perre, P. (1988). Nosomial transmission of HIV in Africa: What tribute is paid to contaminated blood transfusions and medical injections. *Infect. Control Hosp. Epidemiol.* 9: 200-203.

Levenson, R. L., and Mellins, C. A. (1992). Pediatric HIV disease: What psychologists need to know. *Prof. Psychol. Res. Prac.* 23: 410-415.

Lifschitz, M., Hanson, C., Wilson, G., and Shearer, W. T. (1989). Behavioral changes in children with human immunodeficiency virus (HIV) infection. *V Int. Conf. AIDS Abstr.* 5: 316.

Liss, M., and Younkin, S. (1987). *Pediatric AIDS: The relationship between knowledge and policy.* Paper presented at the annual meeting of the American Psychological Association, New York.

Loveland, K. A., and Stehbens, J. (1990). Early neurodevelopmental signs of HIV infection in children and adolescents. In Kozolowski, P. B., Snider, D. A., Vietze, P. M., and Wisniewski (eds.), *Brain in Pediatric AIDS*, Karger, Basel, pp. 72-79.

Loveland, K. A., Stehbens, J., Contant, C., Bordeaux, J. D., Sirois, P., Bell, T. S., and Hill, S. (1994). Hemophilia growth and development study: Baseline neurodevelopmental findings. *J. Pediatr. Psychol.* 19: 223-239.

Luzuriaga, K., McQuilken, P., Somasundara, M., Hesselton, R., and Sul, J. L. (1993). Early viremia and immune responses in vertical human immunodeficiency. *J. Infect. Dis.* 167: 1003-1013.

Mangos, J. A., Doran, T., Aranda-Naranjo, B., Rodriguez-Escobar, Y., and Scott, A. (1989). Pediatric AIDS: A new health problem on the Texas horizon. *Tex. Med.* 85: 34-36.

Mangos, J. A., Doran, T., Aranda-Naranjo, B., Rodriguez-Escobar, Y., Scott, A., and Setzer, J. R. (1990). Pediatric AIDS: Psychosocial impact. *Tex. Med.* 86: 40-42.

Marzuk, P. M., Tierney, H., Tardiff, K., Gross, E. M., Morgan, E. B., Hsu, M. A., and Mann, J. J. (1988). Increased risk of suicide in persons with AIDS. *J. Am. Med. Assoc.* 259: 1333-1337.

McCollum, A. T. (1975). *The Chronically Ill Child: A Guide for Parents and Professionals*, York University Press, New Haven.

Myers, A., and Weitzman, M. (1991). Pediatric HIV disease: The newest chronic illness of childhood. *Pediatr. Clin. North Am.* 38: 169-194.

Miles, S. A., Balden, E., Magpantay, L., Wei, L., Leiblein, A., Hofheinz, D., Toedter, G., Stiehm, E. R., Bryson, Y., and The Southern California Pediatric AIDS Consortium (1993). Rapid serologic testing with immune-complex-dissociated HIV p24 antigen for early detection of HIV infection in neonates. *New Engl. J. Med.* 328: 298-302.

Morgan, G., Wilkins, H. A., Pepin, J., Jobe, O., Brewster, D., and Whittle, H. (1990). AIDS following mother-to-child transmission of HIV-2. *AIDS* 4: 879-882.

Morrow, A. L., Benton, M., Reves, R. R., and Pickering, L. K. (1991). Knowledge and attitudes of day care center parents and care providers regarding children infected with human immunodeficiency virus. *Pediatrics* 87: 876-883.

Msellati, P., Lepage, P., Hitimana, D. G., VanGoethem, C., Van de Perre, P., and Dabis, F. (1993). Neurodevelopmental testing of children born to human immunodeficiency virus type 1 seropositive and seronegative mothers: A prospective cohort study in Kigali, Rwanda, *Pediatrics* 92: 843-848.

Muller, O., Musoke, P., Sen, G., and Moser, R. (1900). Pediatric HIV-1 disease in a Kampala hospital. *J. Trop. Dis.* 36: 283-286.

NIAID (1994). Cited in *AIDS Soc. Int. Res. Pol. Bull.* (1994, June/July), 5(4): 3.

National Institute of Child Health and Human Development Intravenous Immunoglobulin Study Group. (1990). Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. *New Engl. J. Med.* 325: 73-80.

Navia, B. A., Cho, E., Petito, C. K., and Price, R. W. (1986). The AIDS dementia complex: II. Neuropathology. *Ann. Neurol.* 19: 525-535.

Newton, E. A. C., White, F. M. M., Sokal, D. C., King, T. D. N., and Forsythe, S. S. (1994). Modeling the HIV/AIDS epidemic in the English-speaking Caribbean. *Bull. Pan Am. Health Org.* 28(3): 239-249.

Nozyce, M., Hoberman, M., Arpadi, S., Wiznia, A., Lambert, G., Dobroszycki, J., Chang, C. J., and St. Louis, Y. (1994). A 12-month study of the effects of oral zidovudine on neurodevelopmental functioning in a cohort of vertically HIV-infected inner-city children. *AIDS* 8: 635-639.

Oleske, J. M. (1990a). Diagnostic criteria of pediatric AIDS. In Kozlowski, P. B., Snider, D. A., Vietze, P. M., and Wisniewski (eds.), *Brain in Pediatric AIDS*, Karger, Basel, pp. 13-17.

Oleske, J. (1990b). Human immunodeficiency virus testing of sexually abused children and their assailants [letter]. *Pediatr. Infect. Dis. J.* 9(1): 67.

Oleske, J., Minnefor, A., Cooper, R., Thomas, K., Cruz, A., Ahdieh, H., Guerrero, I., Joshi, V. V., and Desposito, F. (1983). Immune deficiency syndrome in children. *J. Am. Med. Assoc.* 249: 2345-2349.

Olofsson, M. (1989). Children and AIDS. *Nordisk Med.* 104: 80-82.

Patrascu, I. V., Constantinescu, St. N., and Dublanchet, A. (1990). HIV-1 infection in Romanian children. *Lancet* 335: 672.

Peckham, C. S., and Newell, M. L. (1990). HIV-1 infection in mother and babies. *AIDS Care* 2: 201-211.

Pearson, D. A., and Pumariega, A. J. (1991). The development of psychiatric symptomatology in patients with cystic fibrosis. *J. Am. Acad. Child Adol. Psychiatry* 30: 290-297.

Perry, S. W. (1990). Organic mental disorders caused by HIV: Update on early diagnosis and treatment. *Am. J. Psychiatry* 147: 696-710.

Petito, C. K. (1988). Review of central nervous system pathology in human immunodeficiency virus infection. *Ann. Neurol.* 23(suppl): S54-S57.

Piaget, J., and Inhelder, B. (1969). *The Psychology of the Child*, Basic Books, New York.

Piot, P., and Tezzo, R. (1990). The epidemiology of HIV and other sexually transmitted infections in the developing world. *Scand. J. Infect. Dis. Suppl.* 69: 89-97.

Pizzo, P. A., Butler, K., Balis, F., Brouwers, E., Hawkins, M., Eddy, J., Einloth, M., Falloon, J., Husson, R., Jarosinskki, P., Meer, J., Moss, H., Poplack, D. G., Santacroce, S., Wiener, L., and Wolters, P. (1990). Dideoxycytidine alone and in an alternating schedule with zidovudine in children with symptomatic human immunodeficiency virus infection. *J. Pediatr.* 117: 799-808.

Pizzo, P. A., Eddy, J., and Falloon, J. (1988a). Acquired immune deficiency syndrome in children. *Am. J. Medicine*, 85(suppl 2A): 195-202.

Pizzo, P. A., Eddy, J., Falloon, J., Balis, F. M., Murphy, R. F., Moss, H., Wolters, P., Brouwers, P., Jarosinski, P., Rubin, M., Broder, S., Yarchoan, R., Brunetti, A., Maha, M., Nusinoff-Lehrman, S., and Poplack, D. G. (1988b). Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *New Engl. J. Med.* 319: 889-896.

Preble, E. A. (1990). Impact of HIV/AIDS on African children. *Social Sci. Med.* 31: 671-680.

Pressman, H (1992). Communication disorders and dysphagia in pediatric AIDS. *J. Am. Speech Lang. Hear. Assoc.* January, 45-47.

Price, R. W., Brew, B., Distis, J., Rosenblum, M., Scheck, A. C., and Cleary, P. (1988). The brain in AIDS: Central nervous system HIV-1 infection and AID dementia complex. *Science* 239: 586-592.

Price, D. B., Inglese, C. M., Jacobs, J., Haller, J. O. Kramer, J., Hotson, G. C., Loh, J. P., Schlusselberg, D., Menz-Bautista, R., Rose, A. L., and Fikrig, S. (1988). Pediatric AIDS: Neuroradiological and neurodevelopmental findings. *Pediatr. Radiol.* 18: 445-448.

Prover, C. G., and Gershon, A. A. (1991). Medical management of newborns and infants born to human immunodeficiency virus-seropositive mothers. *Pediatr. Infect. Dis. J.* 10: 684-695.

Public Health Service/NIH News Release. "Interim results lead to discontinuation of AZT-only study arm." AIDS Clinical Trial Group Protocol 152, February 3, 1995.

Rudin, C., Berger, R., Toble, R., Nars, P. W., Just, M., and Pavic, N. (1990). HIV-1, hepatitis (A, B, and C), and measles in Romanian children. *Lanet* 336: 1592-1593.

Ruff, A. J., Quinn, T. C., and Halsey, N. A. (1990). The impact of AIDS on allocation of resources in developing countries. *Pediatr. AIDS HIV Infect. Fetus Adol.* 1: 55-58.

Ryder, R. W. (1992). Difficulties associated with providing an HIV-free blood supply in tropical Africa. *AIDS* 6: 1395-1397.

Ryder, R. W., Nsuami, M., Nsa, W., Kamenga, M., Badi, N., Utshudi, M., and Heyward, W. L. (1994). Mortality in HIV-1-seropositive women, their spouses and their newly born children during 36 months of follow-up Kinshasa, Zaire. *AIDS* 8: 667-672.

Sahler, J. Z., and Friedman, S. B. (1981). The dying child. *Pediatr. Rev.* 3: 159-165.

Sarafino, E. P. (1979). An estimate of nationwide incidence of sexual offenses against children. *Child Welf.* 58: 127-134.

Schill, P. H., Bruneau, B., LePage, B., Humeau, O., Grimault, C., Tampreau, V., Blanchard-de Vaucouleurs, A., and Buisson, Y. (1989). Etude de la seroprevalence des anticorps anti-VIH dans une population rurale haitienne. *Bull. Soc. Pathol. Exot. Fil.* 82: 308-315.

Scott, G. B., Hutto, C., Makisch, R. W., Mastrucci, M. T., O'Connor, T., Mitchell, C. D., Trapido, E. J., and Parks, W. P. (1989). Survival in children with perinatally acquired human immunodeficiency virus Type 1 infection. *New Engl. J. Med.* 321: 1791-1796.

Seibert, J. M., Garcia, A., Kaplan, M., and Septimus, A. (1989). Three model pediatric AIDS programs: Meeting the needs of children, families and communities. In Seibert, J. M.,

and Olsen, R. A. (eds.), *Children, Adolescents and AIDS*, University of Nebraska Press, Lincoln, NE, pp. 25-60.

Shaffer, N., Hedberg, K., Davachi, F., Lyamba, B., Breman, J. G., Masisa, O. S., Behets, F., Hightower, A., and Nguyen-Dinh, P. (1990). Trends and risk factors of HIV-1 seropositivity among outpatient children, Kinshasa, Zaire. *AIDS* 4: 1231-1236.

Shaw, G. M., Harper, M. E., Hahn, B. H., Epstein, L. G., Gajdusek, D. C., Price, R. W., Navia, B. A., Petito, C. K., O'Hara, C. J., Groopman, J. E., Cho, E., Oleske, J. M., Wong-Staal, F., and Gallo, R. C. (1985). HTLV-III Infection in brains of children and adults with AIDS encephalopathy. *Science* 227: 177-182.

Sirois, P. A., and Hill, S. D. (1993). Developmental change associated with human immunodeficiency virus infection in school-age children with hemophilia. *Devel. Neuropsychol.* 9: 177-197.

Smith, D. G. (1990). Thailand: AIDS crisis looms. *Lancet* 335: 781-782.

Sparrow, S., Balla, D., and Ciccetti, D. (1984). *Vineland Adaptive Behavior Scales*, American Guidance Service, Circle Pines.

Spiegal, L., and Mayers, G. (1991). Psychosocial aspects of AIDS in children and adolescents *Pediatr. Clin. North Am.* 38: 153-167.

Thorndike, R. L., Hagen, E. P., and Sattler, J. M. (1986). *Guide for Administering and Scoring the Stanford-Binet Intelligence Scale* (fourth edition), Riverside Publishing Company, Chicago, IL.

Ultmann, M. H., Belman, A. L., Ruff, H. A., Novick, B. E., Cone-Wesson, B., Cohen, H. J., and Rubinstein, A. (1985). Developmental abnormalities in infants and children with Acquired Immune Deficiency Syndrome (AIDS) and AIDS-related complex. *Devel. Med. Child Neurol.* 27: 563-571.

Ultmann, M. H., Diamond, G. W., Ruff, H. A., Belman, A. L., Novick, B. E., Rubinstein, A., and Cohen, H. J. (1987). Developmental abnormalities in children with acquired immunodeficiency syndrome (AIDS): A follow-up study. *Int. J. Neuroscience*, 32: 661-667.

Walker, D. W., and Hulecki, M. B. (1989). Is AIDS a biasing factor in teacher judgment? *Except. Child.* 55: 342-355.

Waters, B. G. H., Ziegler, J. B., Hampson, R., and McPherson, A. H. (1988). The psychosocial consequences of childhood infection with human immunodeficiency virus. *Med. J. Austr.* 149: 198-201.

Weisglas-Kuperus, N., Uleman-Vleeschdrager, M., and Baerts, W. (1987). Ventricular haemorrhages and hypoxic-ischemic lesions in preterm infants: Neurodevelopmental outcome at 31/2 years. *Devel. Med. Child Neurol.* 28: 623-629.

Weller, B. F. (1994). The second decade in South East Asia. *Nurs. Stand.* 8(28): 42-43.

Whitt, J. K., Hooper, S., Tennison, M. B., Robertson, W. T., Gold, S. H., Burchinal, M., Wells, R., McMillan, C., Whaley, R. A., Combest, J., and Hall, C. D. (1993). Neuropsychologic functioning of human immunodeficiency virus-infected children with hemophilia. *J. Pediatr.* 122: 52-59.

Wilkinson, G. S. (1993). *Wide Range Achievement Test-3 Administration Manual*, Wide Range, Inc., Wilmington, DE.

Williamson, W. D., Desmond, M. M., Wilson, G. S., Andrew, L., and Garcia-Prats, J. A. (1982). Early neurodevelopmental outcome of low birth weight infants surviving neonatal intraventricular hemorrhage. *J. Perinat. Med.* 10: 34-41.

Wirt, R. D., Lachar, D., Klinedinst, J. K., and Seat, P. D. (1984). *Multidimensional Description of Child Personality: A Manual for the Personality Inventory for Children* (revised edition), WPI, Los Angeles.

Wolters, P. A., Brouwers, P., Moss, H. A., and Pizzo, P. A. (1994). Adaptive behavior of children with symptomatic HIV infection before and after zidovudine therapy. *J. Pediatr. Psychol.* 19: 47-61.

Working Group on Mother-to-Child Transmission of HIV. (1992). Methodological issues in mother-to-child transmission of HIV. *VIII International Conference on AIDS/III STD World Congress* [abstract PoC4218].

World Health Organization (1995, January 13). The current global situation of the HIV/AIDS pandemic. *Weekly Epidemiol. Rec.* 7-8.

Willoughby, A. (1994). Epidemiology of human immunodeficiency virus infection in children. *Ann. All.* 72: 185-193.

Ziegler, J. B., Cooper, D. A., Johnson, R. O., and Gold, J. (1985). Postnatal transmission of AIDS-associated retrovirus from mother to infant. *Lancet* 1: 896-897.