

## Medical management of children with HIV infection

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**A**CQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) is the symptomatic end stage of infection with the human immunodeficiency virus (HIV). The HIV epidemic is sustained and continues because of intravenous drug use and sexual spread both heterosexually and homosexually. Currently, children become infected through perinatal exposure to their HIV-infected mothers. Older children and adolescents can acquire HIV through sexual abuse. Prior to March 1985, a limited number of individuals were infected because of exposure to contaminated blood or blood products. This last mode of acquisition is in large part under control in countries that screen blood donors.

An important question for public health in the United States is whether this epidemic will sustain itself in populations where there is predominantly heterosexual spread, as in Africa, or whether less transmission will occur as it moves from areas of high drug use, as with Hepatitis B. In Newark, New Jersey, we have both intravenous drug use and heterosexual spread. Between 1982 and 1984, we noted that most women who had an HIV-infected child were intravenous drug users. However, by 1989 almost half of the women with an HIV-infected child did not use drugs, and their only HIV risk factor was heterosexual contact with an HIV-infected male (Palumbo et al. 1988). Other than in the homosexual community, HIV infection is linked to poverty and drug use, with women of childbearing age usually being infected. Among the minority, poor populations who are disproportionately infected with HIV, the issue of limited access to health care has always existed. The HIV epidemic has simply focused this inequity in health care — especially for women and their children.

The first dilemma faced by the pediatrician caring for children at risk for HIV infection is that of accurate and timely diagnosis. The classical means of identifying HIV-infected patients is by serology (ELISA confirmed by Western blot). However, all infants born to infected

women will have passively (i.e., maternally) acquired HIV antibody lasting for up to 15–18 months (Ryun et al. 1987).

It is estimated that maternal-infant transfer of HIV occurs with an incidence of 25–50% (Scott et al. 1985; Mok et al. 1987; Semprini et al. 1987). The timing of viral infection from mother to offspring currently is under study, but evidence supports both fetal and perinatal transfer. There are new diagnostic assays under development that may be able to differentiate the infant who is truly HIV-infected at birth from the infant with only passive maternal HIV antibody. These include antigen detection, improved viral cultures, detection of viral genetic material in mononuclear cells (polymerase chain reaction or PCR) (Ou et al. 1988; Rogers et al. 1989), and determination of antibody production in newborn serum or immune cells. The ability to detect HIV-infected infants will assist in identifying those who should receive antiviral therapy with drugs such as AZT. By 1991, there may be more than 20,000 HIV-infected children in the United States, and by the year 2000 more than one million infected women and children worldwide (Oleske 1990).

### Clinical Spectrum

The HIV-infected infant and child suffers from a chronic condition with multiorgan system involvement. Nonspecific findings related to chronic viral infection, malnutrition, and immunodeficiency are common. These findings include:

1. Fever
2. Failure to thrive
3. Diffuse adenopathy
4. Hepatosplenomegaly
5. Chronic diarrhea
6. Dermatitis.

Given the history of a child living in a high-risk area for HIV, serology should be performed as part of the evalu-

ation of children who present with these findings. Therapy for such children is mostly supportive. Therapeutic protocols currently are being developed and implemented with the aim of specifically treating HIV infection as early as possible in an attempt to prevent symptomatology or its progression.

Opportunistic infections related to the immunodeficiency caused by HIV are varied and frequently difficult to treat. Opportunistic diseases that should alert one to the possibility of HIV infection regardless of past history include:

1. Persistent oral thrush
2. Recurrent parotid swelling
3. *Pneumocystis carinii* pneumonia (PCP)
4. Other AIDS-defining infections (e.g.: cryptosporidium, atypical mycobacteria)
5. Chronic interstitial pneumonia
6. Unexplained encephalopathy
7. Unusual cancers (Cooper et al. 1988; Falloon et al. 1989).

As the full spectrum of HIV infection in children is understood, involvement of other organ systems has been recognized. There are now well-defined HIV-related diseases of the heart, lung, brain, kidney, liver, CNS, skin, GI tract, eye, and endocrine system of children.

*Pneumocystis carinii* pneumonia (PCP) followed by lymphocytic interstitial pneumonia (LIP) are the two most common opportunistic diseases of HIV-infected children. Fortunately, we have medications for the treatment and prophylaxis of PCP, and there are supportive therapies for LIP. Unfortunately, neurological disease which results in developmental delay eventually occurs in more than 80% of HIV-infected children (Mintz et al. 1989). Except for specific antiviral drugs like AZT (which is not yet approved for children), there is no therapy for HIV encephalopathy.

Perhaps one of the hallmarks which differentiates HIV-infected children from adults is the frequency of bacterial infections. Children have common bacterial infections that are more recurrent and severe. This has led to the use of intravenous gamma globulin in several centers as a preventive measure. Also, there are a number of less common opportunistic infections in children. Some, like disseminated candida infections, can be treated effectively with antimicrobial agents, while others, such as cytomegalovirus or mycobacterium avian intracellulare (MAI), can be diagnosed but have no effective or safe therapies. Many opportunistic diseases seen in HIV-infected children exacerbate preexisting malnutrition. This is especially true for diseases which attack the GI tract, including MAI and viruses which result in nonspecific villous atrophy, the end result being intractable diarrhea and malabsorp-

tion. Diffuse arteritis, which has been described recently in children, can be a cause of multiple organ system failure.

As children survive longer with supportive care and the investigational use of antivirals such as AZT, we can expect other manifestations to appear. Children with HIV infection now have a well-recognized risk to develop cardiomyopathy associated with left-sided heart failure. For any child who survives with an immunodeficiency, malignancies are difficult opportunistic diseases which have been diagnosed in HIV-infected children. In particular, we have seen predominantly B-cell lymphomas of the CNS, malignant degeneration of lymphocytic interstitial pneumonia, rare cases of Kaposi's sarcoma, including two with predominantly cutaneous involvement, and a rare case of disseminated leiomyosarcoma (Joshi and Kauffman 1987).

Besides these unusual organ system diseases seen in HIV-infected children, there has been a resurgence of previously controlled diseases such as congenital syphilis. Similar to the immunocompromised childhood cancer patient, the child with HIV can have fatal infections with common childhood illness such as measles and varicella.

## Treatment

Considering the health complications of the HIV-infected child, including the chronic nature and multi-organ system involvement, it is not surprising that these children frequently are on multiple medications. Many of these regimens are unfamiliar to the pediatrician supervising the care of these children. The risk of adverse drug interactions has become a real problem in managing the health care of these patients. This will only become more severe as investigational drugs are added to these multidrug regimens.

Despite all these difficulties, we have an obligation to treat HIV-infected children to the best of our ability. Twenty years ago, 95% of children with leukemia died. Today, up to 85% are cured, and the intense effort to control childhood leukemia should be the template for our efforts to treat HIV-infected children. This effort to improve the quality of life while working toward a cure will require a multidisciplinary approach including medicine, dentistry, nursing, social work, nutrition, pharmacy, and developmental specialists.

The patients infected with this virus must be the center of this effort, but their families also must be taken into consideration. Almost 40% of children followed by our Children's Hospital AIDS Program (CHAP) are in foster or adoptive care, or frequently are cared for by a member of the extended family (Boland et al. 1988). For example, support services may be required by grandmothers, aunts, or foster families caring for a multiply

handicapped, fragile baby. This is a population of children who often are born to minority families in poor socioeconomic areas. The multidisciplinary team frequently must assume the role of advocate, or encourage patient and family advocacy of these children. Ideally, HIV-infected children and their mothers should receive their health and social care "under one roof," but this usually is not the case. Both the natural mother and foster care families need access to respite care, day care, and hospice services. In many cases, the health care team is the only support available to help the family cope with a dying child.

Another important obligation of any multidisciplinary team providing care to children and their families is education. This educational effort needs to be directed to communities currently having cases and those at risk of having an increase in HIV-infected children. Poverty and drug abuse may now be the major cause of this disease in women and children, but it should not be forgotten that sex and drug use are not confined to the poor. Educational efforts also must be directed to the health care and social service professions. This effort must begin now if we are to have sufficient staff to deal with an ever-increasing number of HIV-infected men, women, and children.

The combination of intravenous drug use together with the heterosexual spread of the virus puts a whole generation of our maturing children at risk for HIV infection. Educational efforts alone have not prevented the spread of this disease to our adolescent children who are at special risk as a group because of their natural behavior patterns. The simple slogan "just say no" is, for many, not enough. Our efforts to prevent this disease in succeeding generations of adolescents must begin well before puberty.

The medical and dental treatment of the HIV-infected infant and child begins with good supportive care (Oleske et al. 1989). This care includes aggressive nutritional management, early treatment of recognized infections, prophylaxis for opportunistic infections (especially PCP), and in children with documented recurrent bacterial infections, regular monthly doses of intravenous gamma globulin. Persistent oral thrush fre-

Nutritional support
Treatment/prophylaxis of HIV-related infection
Immune support with IV gamma globulin
Treatment of end organ failure and chronic pain
Dental hygiene, prophylaxis, and treatment
Psychosocial support of the child and family
Education

**Fig 1.** Supportive care of HIV-infected infants and children.

quently requires aggressive therapy. Intraoral recurrent herpetic infections and aphthous ulcers are common and may reduce caloric intake and hydration. Because of neurological and medical complications, maintenance of oral hygiene often becomes the responsibility of the extended family member. Proper instruction and prevention is a very important educational consideration. Without dental care, the oral cavity can become a source of life-threatening infection. Any possible source of infection within the oral cavity should be treated aggressively. A major area of need is access to regular dental care for the older HIV-infected child.

Physicians have developed the symptomatic care of HIV-infected children to the point that prolonged survival and improved quality of life are measurable. The challenge of pediatric HIV treatment centers is to make available investigational antiviral, immunosupportive, and antiopportunistic infection therapies. While adults may have as long as a 10-year or greater latency period from infection to onset of symptoms, most perinatally HIV-infected children will die within two years of diagnosis. The major requirements for an effective anti-HIV drug is that it prevent activation of latent virus and inhibit HIV replication and spread. Such a drug must penetrate all organ systems, including the CNS, and, since it probably will need to be taken chronically (perhaps lifelong), it must have acceptable toxicity and be able to be taken orally at intervals to ensure effective therapy and patient compliance. AZT is the first of what will need to be a series of antiviral drugs utilized in HIV-infected children. It will probably be at least five years before we have reliable and safe anti-retroviral drug

<b>PCP</b> TMP-SMZ Pentamidine Dapsone* Trimetrexate*	<b>Candida</b> Amphotericin B Ketoconazole Nystatin
<b>Cytomegalovirus</b> Ganciclover* (DHPG)	<b>LIP</b> Oxygen Steroids*
<b>Mycobacterium Avian Intracellulare</b> No effective therapy Amikacin*	
<b>Specific Antiretroviral Therapy</b> AZT (Retrovir)* Recombinant CD4* Other Nucleoside Analogs—e.g.: DDI*	
*Denotes experimental therapy	

**Fig 2.** Therapy in HIV-infected children.

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therapy. The development of a vaccine for this infection is expected to be a difficult task based on experience with other animal retroviral diseases. It is possible that if a vaccine is developed, individuals already infected would be candidates to receive immunization in hopes of stimulating their immune system. Figures 1 and 2 outline the supportive and investigational treatment of the HIV-infected infant and child.

Occupational exposure to HIV in most instances is eliminated by the appropriate practice of safety measures and universal precautions as outlined by the CDC. This is in marked distinction to Hepatitis B — all health care workers should receive the Hepatitis B vaccine.

## Comments

It is important that health care providers identify HIV-infected women before they are pregnant. The routine and appropriate care for pregnant women should include HIV testing. Obviously, this testing should be linked to counseling and care for any woman identified as infected. Early identification will improve care for both the woman and her infant. There is a profound need to drop the emotional, moral, and social stigmatization that accompany the diagnosis of HIV infection. It's time the medical community went about the business of taking care of those infected while preventing the spread of this disease to others. Physicians and dentists need to develop compassionate, comprehensive health-care programs to manage, monitor, and continually improve the health status of the HIV-infected patient. All health care professionals need to participate appropriately in the care of those in our population who are HIV-infected, including the children.

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