

INTRODUCTION

AIDS in children has been a sensational but little understood issue. Fear and ignorance have impeded efforts to understand and control the AIDS epidemic in adults, and this has been even more true for children. Children acquire AIDS as a consequence of adult behavior, but they nevertheless have shared general public opprobrium frequently cast on affected patients.

As of 30 March 1987, a cumulative total of 471 children nationwide met the strict criteria established by the Centers for Disease Control (CDC) for Acquired Immunodeficiency Syndrome (AIDS) in children. An untold additional number, perhaps two to three times more, are infected with the Human Immunodeficiency Virus (HIV) but do not meet the CDC criteria. It is not generally appreciated that AIDS is only one of the more severe manifestations of infection with HIV. Other children infected with HIV may fall anywhere on a spectrum from being completely asymptomatic through suffering growth and developmental retardation to having multisystem disease known as AIDS-Related Complex (ARC) involving blood, skin, brain, heart, kidneys, and other organs.

Both future opportunities for control of HIV infection and the possibilities for future disaster lie in the area of heterosexually transmitted infections in adults and their consequences to children. At present, pediatric infections—other than those acquired previously through HIV contaminated blood products—stem largely from mothers who themselves are intravenous drug users or whose partners either abuse drugs or are bisexual. If the virus continues to spread through these groups, there inevitably will be more heterosexual infections and more transmission to infants, both within and without the drug using and bisexual sectors.

The idea for this conference arose from our perception that the attention of the nation needed to be focused on prevention of HIV infection in children and on the difficulties of caring for those children already infected. At the same time, we learned that the Surgeon General was considering convening a workshop specifically to deal with issues arising from pediatric AIDS. Accordingly, a series of meetings took place in the summer and fall of 1986 to plan for a conference. In the subsequent months, approximately 200 people were invited to a closed conference, known as the "Surgeon General's Workshop on Children with HIV Infection and Their Families."

We made a deliberate effort to convene not only clinical and research physicians, but other types of health providers, clergy, economists, educators, media representatives, and parents. Due attention was given to ethnic and geographical representation.

The workshop took place at Children's Hospital of Philadelphia on 6–8 April, 1987. The fifteen papers surveying what is known in the field were presented in plenary session. Following are abstracts of the papers presented in the plenary sessions and summaries of the recommendations from the Work Groups.

The results set out in these pages exemplify a peculiarly American way of problem-solving: to bring together the informed and the interested, to give each a voice, and to form a consensus which avoids extremes.

We believe that these recommendations are both sound and urgent. If we can learn how to deal humanely with HIV-infected children and to prevent new mothers and children from becoming infected, there is still a chance of stopping the AIDS epidemic. For this purpose, the energies of the American people will need to be mobilized in a "moral equivalent of war" to fight against the spread of HIV.

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EXCERPT FROM KEYNOTE ADDRESS

C. Everett Koop, M.D., D.Sc.
Surgeon General, Public Health Service

Nearly five years ago I came to Philadelphia to stand before a similar group of concerned Americans and share my concerns about handicapped children and their families. My opening remarks at that Surgeon General's Workshop noted that our task would not be easy. We were to consider very complex issues, such as the emotional, the moral, the medical, the technological, the social, the psychological, and the financial issues associated with the care for handicapped children. I also mentioned the awesome challenge of putting a dollar value on a human life.

I wish it were not so, but those remarks are just as appropriate today when we consider yet another problem of major proportion to cope with: the consequences of Human Immunodeficiency Virus (HIV) infection in children and adolescents. Five years ago little was known about the nature and extent of AIDS. And although we suspected that children would become involved, it was then far from reality.

A great deal has changed since that time, as you are well aware. Many of you in this audience have contributed to our expanding knowledge about AIDS or are in some way associated with issues related to this deadly disease. As a result you are familiar with its history. As of the beginning of April 1987, there were among children under 13 years of age 471 reported cases that meet the Centers for Disease Control (CDC) criteria for pediatric AIDS and 139 reported cases among adolescents aged 13 to 19. The nearly 500 cases among young children is *double* the number of cases reported only a year ago. Sixty percent of those children have already died.

Unfortunately, we expect the number of infected children to continue to increase dramatically. By 1991, the Public Health Service estimates that 3,000 children will have suffered from the disease and virtually all will die. As frightening as this may sound, the number is undoubtedly underestimated. We know that HIV infection in children has manifestations that are legion; full-blown CDC-definition AIDS is only part of the story. As many as 2,000 additional children are reported to have symptoms of the infection, but do not fit the specific diagnostic criteria.

It has been found that congenitally acquired HIV infection may affect the infant's central nervous system (CNS) and thus may lead to alterations in growth and development—signs and symptoms not previously identified with AIDS.

With recognition of the wide clinical spectrum of HIV infection in children, the CDC has developed a more detailed and exhaustive classification system for the asymptomatic as well as the symptomatic child, the immunologically compromised child, and the children with neurological disease, lung disease, secondary cancer, cardiopathy, and nephropathy. We know this disease has many presentations in children and, as our knowledge expands, our public health surveillance will continue to reflect this knowledge.

The development of blood-screening procedures and methods of heat treating blood-factor products virtually eliminated the risk of new pediatric AIDS cases from blood and blood products. However, some children had earlier acquired

AIDS from contaminated blood. These children and their families also need our attention. The burden suffered by these children, some of whom may also have a severe chronic illness like hemophilia, is enormous.

About two-thirds of pediatric AIDS cases are the result of transmission from infected mother to child. While there are other modes of transmission of infection to children and adolescents—sexual abuse, drug abuse, and sexual intercourse—our major focus in pediatric AIDS must be on transmission from the infected pregnant woman. Most of these mothers are intravenous drug abusers or sex partners of drug abusers or of bisexual men. As the virus continues its spread among the general population, however, a woman's lack of direct involvement with these high risk behaviors will be no guarantee against her infection and transmission to her fetus.

Present information suggests that up to 65% of babies born to infected mothers will contract the disease. The outlook for these children is almost certain death.

Currently, there are almost no programs that provide coordinated, community-based care for pediatric HIV-infected patients. There is a lack of foster care placement for HIV-infected infants and children. Pediatric units are overwhelmed by the social and medical demands of both ill and well children with HIV infection. There are not enough hospital personnel to provide and coordinate multidisciplinary inpatient, outpatient, community care, and just plain hugging and playing with these children. Pediatric house staff in some institutions where the prevalence of AIDS is high are concerned that their neonatal experience is skewed because of the large numbers of neonates with AIDS.

Many of these children also suffer abandonment by the mother and society. Because of the stigma of AIDS, there are fewer foster homes open to these children. In fact there have been virtually impenetrable barriers between them and a whole variety of social and public health services. Our infants and children with this dread disease must be afforded a normal and dignified life. They must be nurtured, helped to grow and develop, allowed to interact with peers, attend school, and encouraged to enjoy and participate in all activities of childhood, despite a shortened life span.

The AIDS epidemic is imposing severe social and economic burdens on many communities. It will take combined resources from all levels of government and the private sector to meet the increasing costs: of care for an expanding patient population; of educational efforts to reduce high risk behaviors; of maintaining an effective research effort for improved prevention, treatment, and cure; of the social support to juveniles with AIDS and their families to secure the most normal and dignified existence possible.

So far I have been focussing on the issues related to children with AIDS and the heartfelt concern we have for these children. Although we have learned a great deal about AIDS in a short time, our knowledge is nevertheless extremely limited. Prudent judgment must continue to guide us. Under all circumstances we must remain committed to providing humane and dignified care, and we must be willing to bear the responsibilities and costs during the short, troubled lives of these children.

Let us look at this profound tragedy from yet another perspective. Why is there pediatric AIDS? The overwhelming majority of children with congenital AIDS have this disease because of parental prenatal behaviors. While AIDS can afflict children at all levels of society, it is occurring disproportionately in those who have the least capacity and resources to cope. Over half of all babies born with AIDS are black with one or both parents infected with AIDS. Another 25 percent

of all babies born with AIDS are Hispanic.

What we are seeing in reference to AIDS, therefore, is more tragic evidence of high-risk pregnancies and births which are most likely to occur among black women . . . who are poor . . . who are not ready for the world of work . . . who may not even have a high school diploma . . . and who do not have ready access to good prenatal and perinatal health care.

This population of young women produces a disproportionate number of low-birth-weight babies. Life for these babies is a struggle from "day one" . . . and many of them never make it to "day two."

This is additional catastrophic news for the black community, already under great economic and social stress. And it's also more evidence of the apparent inability of American society in general to make much headway in helping these young women deal with their own sexuality and their own destinies.

Maternal infection with the HIV is preventable and so too is congenitally acquired AIDS. Assembled here today is a group of national experts from the sciences, the professional community, the government, and the community at-large to address a public health problem of great importance to our nation and to all people of the world. President Reagan has recently called AIDS "Public Health Enemy No. 1." As the Surgeon General of the United States Public Health Service, I am asking you to join with the President to bring all of our skill, expertise, and resolve to focus attention on the broad range of health concerns related to children suffering from AIDS.

Your task for the next several days will be to develop recommendations for a national strategy for reducing the tremendous burden of this devastating condition, especially among our children. I ask that your recommendations give specific attention to the development of an expanded knowledge base, the health resources and services necessary to address the AIDS problem, and the social strategies necessary to assure that our knowledge and resources are best applied in the service of better health for our children.

The recommendations that will emerge from this Surgeon General's Workshop can change attitudes by utilizing calmness, confidence, and clarity in what we say. We must be precise in the use of words lest we exacerbate fear which can only lead to discrimination against children.

In dealing with the specific problems of pediatric AIDS, we need guidelines for our communities to bring together local officials, health professionals, educators, religious leaders, and parents to develop an interdisciplinary, moral, and just approach for the battle against AIDS.

I wish you well and look forward to the fruits of your labors.

You really have the opportunity to make a major contribution to our understanding of pediatric AIDS, and also to the alleviation of some of the burden borne by children with HIV infection and their families.



CITY OF PHILADELPHIA

W. WILSON GOODE
MAYOR

April 6, 1987

CHILDREN WITH HIV INFECTION (AIDS)
AND THEIR FAMILIES WORKSHOP
Philadelphia, PA

TO ALL IN ATTENDANCE:

As Mayor of Philadelphia, I am privileged to extend my best wishes on this most significant workshop, addressing the issue of "Children with HIV Infection (AIDS) and Their Families."

This gathering is a special one, charged with the important task of formulating recommendations to the Surgeon General of the United States, C. Everett Koop, M.D., in helping to set a national policy regarding this growing problem. May all of you in attendance here today be renewed and encouraged in your efforts through the diverse and informative Workshop sessions.

I express my admiration for the commitment and determination of all participants, and I offer my deepest hopes that this workshop will be an unparalleled success in achieving its goals and objectives.

Sincerely,

A handwritten signature in cursive script, reading "W. Wilson Goode".

W. WILSON GOODE
Mayor

WWG:hs

EXCERPTS FROM PRESENTATIONS

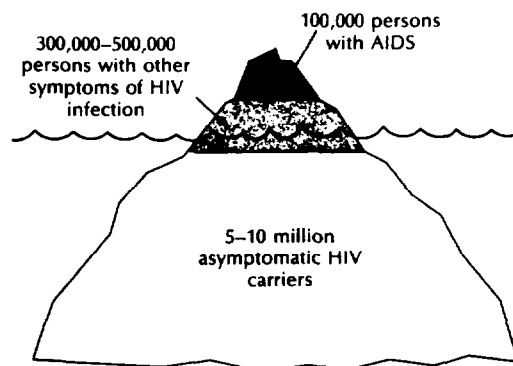
THE GLOBAL EPIDEMIOLOGY OF THE ACQUIRED IMMUNODEFICIENCY SYNDROME

Thomas C. Quinn, M.D.

Introduction

Since its initial recognition in 1981, the acquired immunodeficiency syndrome (AIDS) has become a global pandemic. As of 1 March 1987, nearly 42,000 cases had been reported from over 90 countries. Thirty-two thousand cases have been reported in the United States, an additional 3,000 cases in the other countries of the Americas, 4,500 cases in Europe, and 2,600 cases officially reported in Africa—with several thousand suspected and many more unrecognized in that continent alone. Australia and New Zealand had reported 404 cases for Oceania, and 103 cases had been reported from 10 Asian countries. Because of under-reporting, however, these numbers do not reflect accurately the true incidence of AIDS worldwide. The World Health Organization estimates that there are over 100,000 cases of AIDS throughout the world, with a large majority of these cases occurring in North America and Africa. An additional 300,000–500,000 cases of AIDS-related conditions (ARC) and an estimated 5–10 million people worldwide have already been infected with the virus that causes AIDS, the human immunodeficiency virus (HIV).

Figure 1.



This latter group of infected people represents the human reservoir of this infection from which future cases of AIDS will emerge. In the United States, for example, it is estimated that by 1991 over 270,000 cases of AIDS will have developed from the present pool of 1–2 million HIV-infected individuals. In that year, over 54,000 deaths will occur from AIDS, and AIDS will be ranked as one of the leading causes of premature death in our society. For other areas, particularly Central Africa, where already 10%–15% of the general population has been infected by the AIDS virus, these numbers will be even greater. With conservative estimates of 20%–30% of HIV-infected people developing AIDS within a

five year period, and with an 80% mortality rate two years from time of diagnosis of AIDS, AIDS has clearly established itself as one of the most serious epidemics of the century.

AIDS is characterized by the unusual appearance of life-threatening opportunistic infections or malignancies occurring in an individual who has a severe depression of the cell-mediated immune system. Under this clinical case definition, 31,834 patients (including 31,381 adults and 453 children) have been reported as AIDS cases to the CDC as of 2 March 1987. Of these patients, 18,835 (57% of adults and 61% of children) are known to have died, including over 80% of those patients diagnosed before January 1985. Since the initial reports of AIDS in early 1981, the number of cases reported for each 6-month period continues to increase. However, the increases are not exponential, as evidenced by the lengthening period of time required to double the number of cases.

Cases have now been reported from all 50 States, the District of Columbia, and the 4 U.S. territories. Fifty-three percent of all the cases have been reported from New York and California, and the incidence rate of AIDS for New York City and San Francisco is approximately 100 cases/100,000 population.

Adult Patients

Ninety-seven percent of all adult AIDS patients can be placed in a group that suggests the possible means of disease acquisition. Homosexual or bisexual men not known to have used intravenous drugs represent 65% of all reported cases, or 70% of the male cases. Heterosexual IV drug users comprise 17% of all cases, including 15% of the male cases and 51% of the female cases. Homosexual or bisexual men who have used IV drugs comprise 8% of all cases. Persons with hemophilia or coagulation disorders who have received Factor 8 or Factor 9 concentrates represent 1% of all cases. Heterosexual partners of persons with AIDS or at risk for AIDS represent 4% of all cases, including 2% of the males and 27% of the females. The proportion of female AIDS cases in this risk group increased significantly between 1982 and 1986 from 12% to 27%, a trend which may prove to be a good marker for following patterns in heterosexual transmission. This last category of heterosexual partners also includes those who, without other identifiable risk, were born in countries in which heterosexual transmission is believed to play a major role, such as in Haiti and Africa. Recipients of transfused blood or blood components comprise 2% of all cases, which represents 1% of male cases and 10% of the female. For 3% of AIDS patients, the possible means of disease acquisition is undetermined, in these cases primarily due to lack of epidemiologic investigations before death.

Table 1. *Distribution of Etiologic Risk Factors in AIDS Patients in the U.S.A.*

	<i>Male (93%)</i>	<i>Female (7%)</i>	<i>Total</i>
Homosexual or bisexual men (Non-IVDU)*	70%	—	65%
Homosexual or bisexual men (IVDU)	8%	—	8%
Heterosexual IVDU	15%	51%	17%
Heterosexual partners of persons with AIDS	2%	27%	4%
Coagulation disorders	1%	>1%	1%
Other transfused patients	1%	10%	2%
Undetermined risk factor	3%	11%	3%
	<u>100%</u>	<u>100%</u>	<u>100%</u>

*(IVDU = Intravenous Drug User) (Total 31,381 patients at March 2, 1987)

Pediatric Patients

The percentages displayed in Table 2 have remained fairly constant in the weekly CDC reports. An additional undetermined number of children with evidence of HIV-infection are not included in these numbers because they do not fit the CDC definition for AIDS. These children are defined as having AIDS-related complex (ARC), not a reportable syndrome at this time. Many, if not all, will progress to AIDS.

Table 2. Demographic and Clinical Distribution of Pediatric AIDS Patients <13 years)

AGE:	ETIOLOGIC RISK FACTORS:
(a) < 5 years (88%)	(a) Parent with AIDS or in high-risk category (80%)
(b) > 5 years (12%)	(b) Blood transfusion (12%)
RACE:	(c) Concentrate for coagulation disorders (5%)
(a) Black (57%)	(d) Not known (3%)
(b) Hispanic (22%)	CLINICAL DIAGNOSIS:
(c) White (20%)	(a) Pneumocystis carinii pneumonia (52%)
SEX:	(b) Other opportunistic infection (47%)
(a) Male (55%)	(c) Kaposi's sarcoma (1%)
(b) Female (45%)	
(Total 453 patients at 2 March 1987)	

Pediatric patients have been reported from 29 States, the District of Columbia, and Puerto Rico, with 72% of the pediatric patients reported in Florida, New Jersey, and New York. Since the majority of AIDS cases in children are the results of perinatal transmission from the mother, trends in female AIDS cases may also predict future trends for AIDS in children.

Other Countries

The epidemiology of AIDS in other countries of the Americas, such as Canada and Brazil, and in Europe is quite similar to that described for the United States. The male-to-female ratio is 13:1, and there is a predominance of cases occurring among homosexual or bisexual men and intravenous drug users. However, in tropical countries such as in Africa and Haiti, the male-to-female ratio is 1:1 and the majority of cases are identified among heterosexually active individuals who deny the above risk factors. Currently, an accurate assessment of the exact number of cases and risk factors for transmission among those cases is not entirely feasible, due to these developing countries' lack of resources to support an accurate surveillance system. Serologic surveys for HIV infection and preliminary AIDS surveillance studies using modified case definition, however, have provided useful information regarding the spread of HIV infection and AIDS in these areas.

In areas where international scientific teams have been monitoring AIDS, it is estimated that the annual incidence of AIDS is approximately 200 cases/100,000 population, a rate twice that observed presently in New York City or San Francisco. The male-to-female ratio of AIDS cases in Central Africa is approximately 1:1, and the sex and age-specific distribution of AIDS cases reflects patterns seen with other sexually transmitted diseases in which the incidence and morbidity rates are higher among younger women and older men. Serologic studies have indicated prevalence rates of HIV antibody ranging from 5%-88% for blood donors, 27%-88% among female prostitutes, and 2%-10% among pregnant women of Central Africa. Longitudinal data on HIV seroprevalence have shown a rapid rise in HIV antibodies among prostitutes in Kenya from 4% in 1980 to 59% in 1986. These data demonstrate the rapid spread of HIV infection in a high

risk heterosexually active group in Africa. Exposure to infected blood transfusions and blood-contaminated needles used for medicinal purposes further amplify the transmission of HIV among the general population of these tropical areas. Consequently, the entire Central African population has become at risk, and some natural history studies have already documented there a 1% annual seroconversion rate in a general heterosexual population.

As a result of heterosexual transmission, African women of child-bearing age are exposed to HIV. As in U.S. studies, maternal HIV infection appears to be strongly associated with seropositivity among infants in Africa. In one city of Central Africa, approximately 8% of all infants are born to seropositive mothers. While it is unclear what percent of these children will acquire HIV infection perinatally, it is evident that a substantial number of newborn children are presently being infected with HIV. Children in developing countries are also at risk for acquiring HIV infection from unscreened blood transfusions for the anemia associated with malaria, malnutrition, and other endemic diseases, as well as from exposure to blood-contaminated needles and syringes used for medicinal purposes. Thus, it can be anticipated from these data that HIV infection will have a dramatic effect on the general health of these children and potentially on the safety and efficacy of childhood vaccinations.

New Viruses

This problem in Africa is now being exacerbated by the appearance of additional human retroviruses, referred to as HTLV-IV or LAV-2, or HIV-2, some of which may cause symptomatic disease, including AIDS. Infection with these retroviruses is rapidly spreading throughout West Africa, primarily by heterosexual transmission, blood transfusions, exposure to blood contaminated needles and syringes, and perinatally from mother to infant. Diagnostic assays for HIV-2 are not entirely reliable for detection of infection with these other human retroviruses, and new methods need to be developed rapidly to help control the spread of these retroviruses. Additional studies on the relationship of these human retroviruses to HIV, including genomic and protein comparisons, as well as on the pathogenicity and natural history studies, will help facilitate the development of safe and effective vaccines against these human retroviruses.

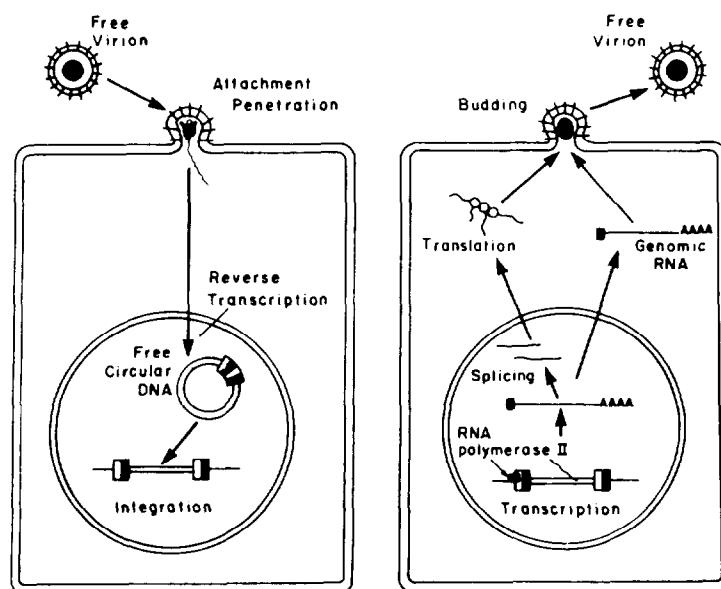
Summary

With an estimated 5–10 million people already infected with HIV, and with projections of 1–2 million cases of AIDS occurring worldwide over the next several years, it is evident that AIDS has clearly become established as a global pandemic, presenting an unprecedented health problem for our society. Unless control efforts are successful, HIV infection will continue to spread rapidly by sexual, parenteral, and perinatal modes of transmission. Until a safe and effective vaccine is available, prevention of HIV transmission must rely primarily on educational programs, modification of sexual practices, screening of blood transfusions, and intensive counseling of seropositive individuals. Faced with one of the greatest epidemics of our lifetime, we must make prevention and control of HIV infection an international public health priority, requiring the full commitment of the necessary political, financial, and professional resources of all countries.

THE HUMAN IMMUNODEFICIENCY VIRUS

Wade Parks, M.D., Ph.D.

The virus etiologically associated with AIDS is a member of the Family Retroviridae. A defining characteristic of this family of viruses is that they have a *diploid* linear single-stranded RNA genome that is surrounded by a protein capsid. The capsid is surrounded by a lipoprotein envelope. This envelope or coat is covered with viral glycoproteins that are involved in viral entry into susceptible cells and is a major target of the host immune system. A unique marker of the Family Retroviridae is the reverse transcriptase which is a part of the virion and which catalyzes the synthesis of DNA from RNA and is thus an RNA-dependent DNA polymerase. The AIDS virus is a member of one of the subfamilies of Retroviridae.



The life cycle of a retrovirus

Figure 1.

The subfamily Lentivirinae that contains the AIDS retrovirus includes a number of unglulate viruses associated with chronic, persistent infections in their natural hosts. These include Equine Infectious Anemia (EIA) or "swamp fever" described first in 1904, Visna—the prototypic lentivirus which causes a neurologic disease of sheep, and Caprine Arthritis and Encephalitis Virus (CAEV). The morphology of lentivirus virions is relatively unique with an elongated, bar-shaped nucleoid. Lentiviruses have a slightly larger genome than most retroviruses, and a larger and more highly variable virion external glycoprotein than other retroviruses. Thus far, the reverse transcriptase differs only slightly, preferring a different divalent cation—magnesium—over manganese.

The etiologic agent of AIDS was originally termed the Lymphadenopathy-Associated Virus or LAV by Luc Montagnier and his co-workers at the Institut Pasteur in Paris. When Robert Gallo and his colleagues at the National Cancer Institute repeatedly isolated virus from AIDS patients, they referred to their isolates as Human T-Lymphotropic Virus type III, or HTLV-III. Gallo and his group had already described an HTLV-I and HTLV-II, human-infecting members of the Family Retroviridae, subfamily oncovirinae. Hence, the etiologic agent of AIDS was called HTLV-III in this country and LAV in Europe and frequently abbreviated HTLV-III/LAV. More recently, a group of virologists have recommended the term, Human Immunodeficiency Virus (HIV), for the AIDS virus.

The retrovirus of AIDS has a structure that is similar to other retroviruses. This means that the linearized form can be depicted as bound on either end by two non-coding regions known as long terminal repeats (LTRs). Moving 5' to 3', the gene order is *gag*, *pol*, and *env* between the LTRs. The *gag* gene encodes for structural proteins of the virus, including the p24 molecule, which is the most abundant polypeptide of the virion and which is very important as a diagnostic marker in infected patients. The *pol* gene encodes for the reverse transcriptase, a remarkable polyfunctional molecule which subserves proteolytic, catalytic, and integration activities within newly infected cells. The *env* gene encodes for the virion surface proteins, which are glycosylated, hence glycoproteins. The transmembrane protein is known as p41E and is the major component of newer recombinant diagnostic seroassays for detecting infection. The external glycoprotein is known as gp120. The gp120 contains the region that forms the attachment to the viral target, the CD4 molecule that characterizes certain T-lymphocytes. This high affinity ligand interaction is the mechanism by which the virus can infect cells. Antibodies to the gp120 can neutralize viral infectivity. The gp120 has multiple regions that are highly variable in genetic sequence; these regions differ from one virus to another. Thus, the virus varies markedly, enabling the virus to avoid elimination by the host's immune system.

Finally, the AIDS retrovirus has some additional genetic features that demonstrate its amazing versatility. Within the virus there are a number of open reading frames that have the capacity to encode for proteins. Two of these have been described: *tat* and *art*. Both are products of spliced mRNAs and appear to subservise important biological roles for viral replication. The *tat* gene especially codes for a protein that binds to a very specific region of the 3-LTR and then enhances transcription. Since the protein can act in trans, it is called the trans activator (*tat*). The *tat* gene product serves to turbocharge the replication of the AIDS retroviruses. Hence, in the short time that an infected lymphocyte may undergo cell division in response to a given antigenic stimulus, *tat* and its related proteins allow maximal production of the retrovirus and thereby increase the probability for successful virus infection of other lymphocytes.

In general, the retrovirus of AIDS is a highly adapted pathogen. Its genetic functions subservise two essential prerequisites for any virus's survival, replication and avoiding immune elimination. A full knowledge of the molecular mechanisms of viral replication and their relevance may be central to the control of the AIDS epidemic.

THE IMMUNOLOGY OF PEDIATRIC AIDS

Arthur J. Ammann, M.D.

The pathogenesis of AIDS, felt to be a result of HIV infection, is best studied in infants and children, since they represent a more pristine host. Undoubtedly, HIV infection and its resultant clinical manifestations are a consequence of infection with this retrovirus as well as the interaction between HIV and other preexisting or subsequent infectious agents. Studies of infants suggest that HIV infection alone may result in impairment of the immune system and secondary susceptibility to opportunistic infection. Even in the case of isolated HIV infection, however, the clinical manifestations and severity of the disease may vary, implying that the time at which infection occurs (as early as 20 weeks gestation), the amount of viral inoculum, and preexisting immunodeficiency are important variables.

Experimental evidence suggests that the monocyte/macrophage may be the initial cell infected with HIV and may subsequently be a major source of continued virus replication and infection. It is important to emphasize that certain organs have significant numbers of monocytes and macrophages that are CD4 receptor-positive (the CD4 receptor is required for HIV infection of cells). This may provide an explanation for the occurrence of the isolated brain and lung involvement sometimes observed in infants with HIV infection. In vitro infection of monocytes with HIV may result in giant cell formation, with a histologic appearance similar to that of the giant cells found in tissue sections obtained from the lung and brain of HIV-infected patients.

The interaction of HIV and other viruses may result in clinical features unique to either adult AIDS or pediatric AIDS. For example, Kaposi's sarcoma—a frequent malignancy in AIDS—has not been convincingly demonstrated in pediatric AIDS. On the other hand, chronic parotid swelling and pulmonary lymphoid interstitial pneumonitis (LIP) are frequently found in pediatric AIDS but rarely observed in adult AIDS.

The pathogenesis of LIP was linked to infection with Epstein-Barr virus (EBV) in several studies which used EBV DNA probes to detect the presence of virus in lung tissue. The response to EBV infection in patients with AIDS is abnormal. In EBV-infected infants with AIDS followed prospectively, virus was cultured for several weeks prior to appearance of antibody to EBV antigen. There was an absence of an IgM anti-VCA response and failure to develop antibody to Epstein-Barr Nuclear Antigen (EBNA). IgG antibody to Anti-Viral Capsid Antigen (VCA) and antibody to Early Antigen (EA) remained high in most patients, suggesting persistent chronic EBV infection. This is in contrast to normal individuals where infection results in an initial increase in antibody to VCA, followed by a decline to low levels which persist for life.

Patients with pediatric AIDS and EBV infection also have prolonged viremia, easily recoverable EBV, and increased numbers of EBV-infected cells. It is possible that the existence of HIV infection in the lung, followed by EBV infection, results in a lymphoid proliferative response manifested as LIP. EBV-infected B cells are more susceptible to HIV infection than uninfected B cells and may be stimulated by HIV antigens to excessive proliferation. A suggested interaction between HIV and EBV was based on observations in EBV-

infected adults who subsequently became infected with HIV and developed additional immunologic abnormalities. The more common sequence of infection in pediatric AIDS, HIV followed by EBV infection, may result in a lymphoproliferative disorder. Adults have a reverse sequence more commonly, and they rarely develop LIP.

The presence of LIP may modify the susceptibility of infants to opportunistic infection. Two studies note that patients with LIP had fewer opportunistic pulmonary infections and that patients with *Pneumocystis carinii* pneumonia (PCP) do not have evidence of pulmonary hyperplasia.

HIV infection of immunocompetent cells may result in immunodeficiency by several mechanisms. Following infection, syncytia formation and fusion of cells occur with subsequent death in vitro. A similar mechanism in vivo could result in T-cell depletion. Cytotoxic T-cells may also destroy infected cells in vivo resulting in reduced numbers of T4 cells and the characteristic reversed T4/T8 ratios seen in most patients. However, early immunologic abnormalities occur prior to depletion of immunocompetent cells, suggesting that HIV infection may directly interfere with immune function. For example, HIV infection of T-cells in vitro results in decreased IL-2 and CD4 receptor mRNA and IL-2 and CD4 receptor expression. It is also known that Peripheral Blood Mononuclear Cells (PBMC) from patients with AIDS and preAIDS have decreased cytokine production in vitro. Many of these cytokines are essential for immune interaction, antiviral, and antitumor effects. Deficiencies of interferon- α (IFN- α), interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), tumor necrosis factor β (TNF- β), interleukin-2 (IL-2), and interleukin-1 (IL-1) have been described. One or more cytokine deficiencies may result in secondary defects, such as abnormal monocyte/macrophage function, decreased natural killer-cell activity, decreased antibody formation, and decreased T-cell immunity.

Abnormalities of macrophage function may play a more critical role in the pathogenesis of HIV-induced immunodeficiency than previously appreciated. The macrophage may act both as a reservoir of HIV infection and, as a result of its central role in the T- and B-cell immunity, may play a primary role in early immunodeficiency.

Immunodeficiency following HIV infection may also result from the immunosuppressive effects of HIV envelope glycoprotein or other immunosuppressive regions of virus proteins. Following HIV infection, envelope glycoproteins are secreted to the surface of cells. Several regions of the envelope glycoprotein are capable of suppressing the immune response in vitro. Glycoprotein 120 (gp120) is capable of binding to the CD4a region of the CD4 receptor and interferes with immune function in vitro as measured by mitogenic and antigenic stimulation.

Prospective studies of patients with AIDS suggest that B-cell abnormalities may precede other laboratory features of immunodeficiency. Patients usually have polyclonal hypergammaglobulinemia. This may result from chronic HIV antigen stimulation or loss of suppressor T-cell regulation. In contrast, antibody levels to HIV antigens are not markedly elevated as is usually observed in other chronic viral infections. Further, specific IgM antibody to HIV is difficult to demonstrate in either acute or chronic infection. As the syndrome progresses, patients lose their ability to respond to other antigens following immunization.

Table 1. B-Cell Abnormalities in AIDS

- Polyclonal hypergammaglobulinemia
 - Failure to produce antibody following immunization
 - Increased spontaneous IgG secretion, due to:
 - 1) antigenic stimulation by HIV
 - 2) increased numbers of EBV infected cells
 - 3) HIV-induced T-cell dependent B-cell activation
 - Decreased B-cell response to antigens
 - Decreased B-cell response to T-cell independent mitogens
-

T-cell abnormalities are numerous and profound. Early abnormalities consist of inability of PBMC to respond to antigens in vitro and of cytotoxic T-cells to kill target cells. In vivo, this correlates with absence of reaction to delayed hypersensitivity skin tests. As the syndrome progresses, PBMC from patients lose their ability to respond to mitogens and alloantigens and are unable to produce normal amounts of essential cytokines (IFN- α , IFN- γ , TNF- α , TNF- β , IL-1, IL-2). The broad-based T-cell deficiencies are most likely a result of both intrinsic abnormalities and severe T-cell depletion.

Table 2. T-Cell Abnormalities in AIDS

Number	Function
■ Lymphopenia	■ Absent delayed hypersensitivity skin tests
■ Decreased T helper cells (decreased H/S ratio)	■ Diminished PBMC response to antigens
■ Decreased T suppressor cells	■ Diminished PBMC response to mitogens (PWM, Con A, PHA)
■ Increased Dr and OKT10 expression on CD8 cells	■ Decreased cytokine production IL-1, IL-2 IFN- α , IFN- γ TNF- α , TNF- β
	■ Decreased Thymic hormones (thymulin)

A number of monocyte defects have been reported in AIDS. Monocytes fail to mature at a normal rate, do not have normal chemotaxis and adherence, and, as determined by use of certain in vitro assays, are unable to kill some microorganisms. An unanswered critical question is whether antigen processing or antigen presentation of HIV-infected macrophages is abnormal.

The major abnormality of the complement pathway which has been described in AIDS is that of increased immune complex formation. This is probably a result of both non-specific polyclonal hypergammaglobulinemia and chronic antigenemia as a consequence of chronic infection with a number of microbial agents. Some of the severe consequences of chronic immune complex formation, such as renal failure, are rarely observed in patients with AIDS. However thrombocytopenia, which is more commonly found, may result from removal of immune complex coated platelets from the circulation.

Table 3. Complement Abnormalities in AIDS

- Increased circulating immune complexes
 - Increased HIV specific immune complexes
 - Immune complex deposition (renal disease, thrombocytopenia)
-

In order to establish a diagnosis of HIV infection, either antibody to HIV or the presence of HIV must be demonstrated. A number of tests for antibody are commercially available. Most of these are enzyme-linked immunosorbent assays (ELISA) and utilize HIV antigens coated on to plastic surfaces to detect IgG antibody in the test serum. The assays are designed to be highly sensitive and therefore readily detect antibody positives, but as a consequence also have a high rate of false positives.

Table 4. Enzyme Linked Immunosorbent Assay (ELISA)

- Method
 - 1) Disrupted virus placed in plastic wells or on plastic beads
 - 2) Incubated with test serum
 - 3) Antibody to antigen detected by enzymatic reaction.
 - Characteristics
 - 1) Sensitive - best for screening
 - 2) High number of false positives
(< 50% are confirmed positive by Western blot)
 - 3) A positive must be confirmed by Western blot
-

It is necessary to confirm each positive by first repeating the ELISA and then, if again positive, confirming the presence of antibody to specific HIV antigens by a Western blot. Other antibody assays include indirect immunofluorescence and radioimmunoprecipitate assays and are primarily for investigational purposes.

A major difficulty in the diagnosis of HIV infection in newborns and infants is the inability to differentiate between passively transferred maternal IgG antibody to HIV and actively produced antibody from the infant. Unfortunately IgM antibody to HIV has been detected only inconsistently. There are several other methods of establishing HIV infection in the infant. Serial antibody testing by Western blot may demonstrate the emergence of new antibodies to HIV antigen. Culture of PBMC for virus or the use of DNA probes may demonstrate presence of HIV, but the methods are currently less sensitive than antibody assays. Newly developed assays for the detection of HIV antigen in serum may provide an alternative means of testing.

A diagnosis in pediatric AIDS can be confirmed using a few well established assays of immunologic function coupled with assays for virus infection or demonstration of viral antigen. The confirmation of HIV infection is essential to provide appropriate care for infected infants and children.

TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN THE UNITED STATES

Martha F. Rogers, M.D.

The human immunodeficiency virus (HIV) is transmitted by three routes: 1) from mothers to infants during the perinatal period, 2) through parenteral exposure to infected body fluids, primarily blood, and 3) through sexual contact. Although other modes of transmission have been proposed, including transmission through casual contact, through insect bites, through exposure to contaminated needles used for tattooing, ear piercing, or acupuncture, and through receipt of hepatitis-B vaccine or immune globulin, there is little or no evidence supporting such occurrence.

Perinatal Transmission

Perinatal transmission accounts nationwide for about three-quarters of cases of HIV infection in prepubertal children. The epidemiologic characteristics of these children closely parallel those of heterosexual adults with AIDS, particularly women. Over half (65%) of reported cases of AIDS in women, 69% of heterosexual men with AIDS, and 73% of the perinatally acquired AIDS cases in children were related to IV drug abuse or sexual contact with IV drug abusers. The geographic areas most affected by heterosexual and perinatal transmission have been the New York City metropolitan area, northern New Jersey, and southern Florida. The majority of heterosexual men (74%), women (72%), and children with perinatally acquired infection (88%) have been black or Hispanic. Most are inner-city dwellers of low socioeconomic status.

Evidence suggests that perinatal transmission can occur by three modes: 1) transplacental passage of the virus in utero, 2) exposure to infected maternal blood and vaginal fluids during the labor and delivery of the infant, and 3) post partum ingestion of breast milk containing the virus. The proportion of perinatally acquired cases attributable to each of these modes is unknown.

Preliminary data from prospective studies of infected women and their infants indicate that the frequency of transmission from mothers to their infants may be as high as 50%. Both symptomatic and asymptomatic women can transmit HIV to their infants. The risk factors associated with transmission, however, have not been defined. Mothers can transmit HIV in more than one pregnancy. Each infected infant is at risk of developing AIDS.

Table 1. Possible Risk Factors for Transmission of HIV from Mothers to Their Infants

Viral factors—viremia, latent vs. active infection, % cells infected
Substance abuse or other environmental/behavioral factors
Other infections present
Level of immune suppression
Continued exposure to HIV
Host factors

These prospective studies also indicate that maternal HIV infection is probably not associated with adverse prenatal or neonatal infant outcomes, nor with an increase in obstetrical complications. Two studies have reported an increased frequency of spontaneous abortions among seropositive women, but three other studies have not observed this trend. To date none of the women in the CDC Classification-3 or less developed AIDS during the pregnancy. In one study, however, a trend towards an increased incidence of hospitalizations for infections in seropositive versus seronegative pregnant women was observed. In addition, a greater proportion of seropositive pregnant women developed complications during an average of 6 months' follow-up postpartum, compared with seropositive women who did not become pregnant and who were followed an average of 12 months.

Parenteral Transmission

Transmission through parenteral exposure to infective body fluids has occurred primarily in 2 populations: 1) in persons sharing contaminated needles used to inject illicit drugs, and 2) from donors to recipients of blood or blood products. Transmission through accidental injuries with contaminated needles or other cutting objects in the health care setting has been extremely rare, occurring in less than 1% of such injuries.

About one-fifth of reported AIDS cases are attributable to transmission through use of contaminated needles for injecting illicit drugs. Seventy-four percent of these patients come from New York and New Jersey. Seroprevalence studies of IV drug abusers have shown infection rates of up to 70% in these areas, 42% in Boston, 11% in Chicago, and 10% in San Francisco. Several studies have shown that in IV drug abusers, seroprevalence is highest in those who are black or Hispanic.

Transmission through receipt of infected blood or blood products accounts for 3% of adult and 17% of the pediatric AIDS patients nationwide. Cases are scattered throughout the United States with California and New York having the greatest number of cases. Most of the children with transfusion-acquired AIDS were transfused in the neonatal period or had coagulation disorders.

No cases of transfusion-acquired AIDS have been reported in children transfused after initiation of donor screening for HIV antibody in March–April 1985. Although transmission through transfusion of seronegative blood can occur when the donor is in the early stages of HIV infection and is viremic but not yet producing antibody, this has been rare.

In one study of the recipients of blood collected prior to HIV screening from donors who later developed AIDS, the risk of HIV infection following receipt of blood from an infected donor approached 100%. In instances of split donations, in which one recipient became infected, so did the other. Once a seropositive donor transmitted the virus to a recipient, all subsequent recipients of blood from that donor also became infected.

Although donor screening procedures and heat treatment of coagulation products have markedly reduced the transmission of HIV through these routes, cases of AIDS in persons who received these products before these interventions will continue to occur. The incubation period for AIDS in adults with transfusion-acquired infection averages 3 years and has been as long as 7 years. The incubation is shorter for children, averaging 2 years and ranging up to 6 years.

Sexual Transmission

Sexual contact is the most common mode of HIV transmission in adults, and accounts for over three-quarters of reported cases. Sexual contact between homosexual or bisexual men has accounted for 95% of sexually acquired HIV infection, but heterosexual transmission is increasing, particularly in minority populations. In contrast to gay male cases, about three-quarters of women with AIDS and of heterosexual men with AIDS are black or Hispanic.

The frequency of transmission between heterosexual sex partners is around 10%–15% in the partners of hemophiliac men and transfusion recipients, about 40% in the non-drug-abusing partners of IV drug abusers, and about 58% in a study of partners of primarily IV drug abusers and Haitian immigrants. Some persons have acquired infection after only a few at-risk sexual encounters, while others did not acquire infection despite repeated contact over several years. Medical conditions (such as cervicitis or vaginitis), menstruation, and sexual practices (anal intercourse) that involve greater exposure to blood and friable tissues increase the likelihood of transmission. Transmission has occurred, however, in persons engaging in vaginal intercourse exclusively and without any of the above conditions.

Casual Contact

Transmission through close but nonsexual contact (so called “casual”) has been extremely rare. Only three possible cases have been reported. Two of these cases involved nursing care of bedridden patients associated with extensive and repeated contact with blood and body fluids of the infected patient. The other case involved apparent transmission between two siblings, but the nature of the contact was not well characterized. Nine other independent studies of over 400 family members of HIV-infected patients have not found evidence of household transmission. In addition, none of the family members of the over 30,000 AIDS cases reported to the Centers for Disease Control (CDC) has developed AIDS as a result of household contact.

Intervention methods designed to prevent further spread of HIV infection must consider the epidemiology of the infection including the modes of transmission, the characteristics of the currently affected populations, and the potential for spread within these populations and to other groups.

APPROACHES TO PREVENTION OF HIV INFECTION

Walter R. Dowdle, Ph.D.

The five basic mechanisms for prevention of infectious diseases include 1) immunoprophylaxis (vaccine), 2) chemoprophylaxis/therapy (drugs), 3) sanitation (environment), 4) lifestyle modification (behavior), and 5) vector control. Of these five mechanisms, the first four are applicable to prevention of HIV infection. There is no evidence to suggest that the AIDS virus is transmitted through insect or other vectors.

The first two of the four mechanisms, vaccines and prophylactic/therapeutic drugs, are under development. Ideally, both will be incorporated into future strategies. Much progress has been made toward understanding the basic properties of potential retrovirus vaccines, but 5 to 10 years or more may be required before a vaccine can be realistically considered as a public health tool. How a vaccine will be utilized in prevention strategy will depend upon its availability, cost, efficacy, and safety. Greater promise has been shown for antiviral drugs, particularly as we learn more about the pharmacology and clinical efficacy of certain classes of drugs.

For the present, however, our strategy must rely on the two remaining mechanisms, modifying the environment and modifying personal behavior.

Modifying the environment is of limited benefit, but some changes have already been accomplished. Tests for screening the blood of donors for HIV antibody have been used regularly for nearly two years. This screening has vastly reduced the risk of transfusion-associated infections. Donor screening and treatment of factor VIII has virtually eliminated the risk of AIDS for persons with hemophilia. The environment does not pose a major risk for health care workers. Needlestick injury would appear to be the greatest concern, but recommendations for caution by health care workers have been widely disseminated. Our main task has been to reassure the public that the general environment does not present a threat. The virus is not transmitted through casual social contact or food and water.

The remaining and most important mechanism for prevention consists of modifying behavior. This is a difficult and often controversial task that in the past has not been considered effective for other sexually transmitted diseases (STDs). Nevertheless, we must make a concerted effort to develop effective educational programs regarding HIV infection. Specific mechanisms for modifying behavior include modification of sexual practices of infected persons, routinely offering testing and counseling to persons at high risk, treating IV drug abusers to preclude transmission of the virus through the use of contaminated needles, and information and education programs. There is considerable evidence that risk reduction already has occurred in the gay community.

Effective information/education programs include a whole spectrum of activities, ranging from TV spots to individual counseling sessions. An effective program requires multiple channels of information tailored to specific audiences and delivered through the auspices of a wide range of private and public organizations and institutions. The Public Health Service Information/Education Program is directed to the general public, to school- and college-aged young persons, to other persons at increased risk, and to health workers. The program is budgeted

at over 79 million dollars, with 102 million proposed for next year. The general public can be informed and educated through hotlines, coalitions, ad campaigns, and clearinghouses. That, of course, forms the foundation and background on which more specific programs aimed at high-risk groups can be developed. Each of the nation's school systems will decide how best to implement education in AIDS prevention at appropriate ages. There is less argument here than may appear on the surface. Our interest is in assisting local school groups in developing their own curricula. We are trying to facilitate that activity, but by no means is the Federal government attempting to tell anyone what to teach. The individual school boards will make their own decisions. We do feel that there is great demand and eagerness in the schools to move on the education issue.

Efforts at educating health workers can be productive, because they are a major channel of information to infected patients and in carrying preventive information to others.

When we speak of educating those at increased risk for pediatric AIDS, the preferable strategy is to prevent infection in women of child-bearing age. This is a very difficult area. Those at increased risk are the female sex partners of men at high risk, intravenous drug users, prostitutes and clients. These are difficult to reach. The second line of defense is to provide counseling to those already infected to help them enter into a program of comprehensive health care and follow-up, including avoidance of pregnancy. After that, our options grow less and less clear.

In some geographic areas and for some populations, these information/education activities are beginning. To ensure maximum effectiveness, these programs must be constantly evaluated and modified if necessary. Increased knowledge and general awareness of prevention information is important, but our ultimate criterion of success must be a change in personal behavior that results in decreased transmission of infection.

NATURAL HISTORY OF HIV INFECTION IN CHILDREN

Gwendolyn B. Scott, M.D.

One hundred thirty-four cases of perinatal Human Immunodeficiency Virus (HIV) infection were identified in South Florida between January 1981 and December 1986. Each year since 1981, we've seen an increasing number of cases. In 1986 we identified one-third of our total case load, and so far in 1987 we are seeing at least one new case per week. These infants were born to 109 infected women. Drug abuse accounted for 22% of the disease in the mothers in comparison to 60% reported nationally. Fifty-one of these children meet the CDC surveillance criteria for AIDS; 81 others have clinical symptomatology and are diagnosed as ARC. Two, who are now 7 years old, are asymptomatic.

Ninety-two percent of these children were black. The majority of children presented with clinical disease in the first two years of life (74%). There are, however, a number of children who present between the ages of 2 and 6 with the first manifestations of disease. The overall mortality in these children is 35%, but among those who meet the criteria for AIDS, the mortality is 73.5%.

Pneumocystis carinii pneumonitis (PCP) and *Candida esophagitis* are the most common opportunistic infections. Failure to thrive is the presenting complaint. Lymphadenopathy, hepatosplenomegaly, and persistent oral thrush are some of the more common findings. We have seen disseminated cytomegalic virus infection frequently, five cases of cryptosporidiosis, and one case of *Mycobacterium avium-intracellulare*. Tumors occur, but are rare in children. We have a few cases of Kaposi's sarcoma, one of lymphoma of the liver, and one of Burkitt's lymphoma of the lung. Opportunistic infections presenting in the first year of life are associated with a higher mortality.

In an effort to better describe the clinical outcome of infection in pediatric cases, a syndrome approach has been applied.

Table 1. Syndromes Associated with Pediatric HIV Infection

Wasting Syndrome
Lymphoid Interstitial Pneumonitis
Recurrent Bacterial Infection
Encephalopathy
Lymphadenopathy Syndrome
Cardiomyopathy
Hepatitis
Renal Disease

More than one of these syndromes may occur in the same patient separately or simultaneously. There appears to be a relationship between the immune response and the development of these syndromes. For example, patients with early onset pneumocystis pneumonitis or encephalopathy tend to have decreased evidence of immune response and have a higher mortality. In comparison, patients with LIP, lymphadenopathy syndrome, cardiomyopathy, recurrent bacterial infections, or renal disease generally have a lymphoproliferative response with hyper-

gammaglobulinemia, lymphadenopathy, and hepatosplenomegaly. Children with PCP have an earlier age of onset and a higher mortality rate than those with LIP.

Table 2. *LIP and Early Onset PCP*

	LIP	PCP
Mean Age of Onset	15.8 mos.	6.2 mos.
Median Age of Onset	13.5 mos.	5 mos.
Overall Mortality	25.7%	85.7%

The overall mortality for PCP is 85.7% as compared to 25.7% in the LIP group. The immune response in these groups differs. PCP is associated with a lympho-ablative response, while LIP is associated with a lymphoproliferative response. A greater understanding of the spectrum of disease and knowledge of the natural history of the various syndromes will allow better predictions of prognosis. Although not all HIV infected children die early in life, this is an illness that is unpredictable and is associated with a high rate of morbidity and mortality.

The child is usually the first member of the family that is identified as being infected. In this situation, screening of the parents and siblings is indicated. In the majority of cases, the mother is asymptomatic at the time of diagnosis of HIV infection in her infant. Of the 109 mothers in our patient population, 30% have subsequently developed AIDS or ARC. Seventeen mothers have died.

This series of patients has offered us the opportunity to evaluate the risk of an HIV infected pregnant woman delivering an infected infant. Twenty-three HIV infected women have had 40 subsequent infants after the birth of the index case. Not every subsequent infant will be infected. We have followed one woman who has delivered four infected infants, but another mother had an infected infant and subsequently delivered three uninfected children. Still another had an infected infant, an uninfected one, and then another infected one. We obviously do not know what factors cause a mother to pass the infection on to her infant. Of all the subsequent infants, 52% are infected. This represents a substantial risk for these women and emphasizes the importance of identifying them so they can receive appropriate counselling regarding pregnancy. This population may represent a special population of women, and further studies are underway to determine the risk of having an infected child in an HIV-positive woman who has not had previously infected infants.

In conclusion, pediatric HIV infection presents with a broad spectrum of disease and is associated with a high mortality rate. The majority of children with this disease are black or Hispanic and reside in the lower socioeconomic areas of the inner city. It is important to recognize infected children early so that appropriate instructions for care can be given to the parent and regular medical followup can be instituted. In addition, with the development of anti-viral drugs, early diagnosis and recognition will be imperative, so that early treatment can be given. Screening of the family is important to identify infected family members and to give appropriate counselling and education. The HIV-positive woman is at risk for giving birth to an infected infant. Prevention of perinatal infection will only be accomplished by prevention of disease in women or by other interventions, such as drug therapy. Identification of HIV-positive women is important so that appropriate education and counselling can be provided.

NATURAL HISTORY OF HIV INFECTION II

James Oleske, M.D.

Estimates from the CDC suggest that by 1991 there will be 12.5 million Americans infected with the AIDS virus (Human Immunodeficiency Virus—HIV) and 250,000 of these will be symptomatic AIDS cases. Based on our experience and those of others caring for pediatric AIDS cases, by 1991 there may be 10,000 to 20,000 symptomatic HIV infected infants and children in the USA.

Our difficulties in providing care to over 60 active pediatric AIDS cases at Children's Hospital of New Jersey in Newark indicate major problems in the near future. The health care requirements of infants and children infected with HIV are extensive and include the complex tertiary medical capabilities of a pediatric hospital and intense psychological services. The care we provide to these children includes vigorous nutritional support, including placement when necessary of intravenous catheters, early hospitalization for treatment of possible infection episodes, and monthly replacement therapy with intravenous gamma globulin. Tissue biopsy of lung, lymph nodes, thymus and bone marrow, as well as CAT scan, gallium scan and esophagoscopy are frequent requirements in the clinical evaluation of these children. Research and time consuming investigational drug studies are now being undertaken on our patients. All of these activities—diagnosis, clinical care, and necessary research—have placed an enormous burden on the available resources at our children's hospital. Besides the medical dilemma posed by AIDS, there is the significant public misunderstanding of this disease with ongoing stigmatization of patients and their families.

The development of antibody screening tests has substantially reduced (although not eliminated) the risk of blood transfusion acquired AIDS. It is true that the majority of cases of AIDS in children is due to perinatal exposure from an infected mother, but for the next five to six years we must follow a cohort of newborns who received small blood transfusions in the nursery between 1980 and 1985, and who are at risk of developing this disease. As pediatricians we must insist that we have safe blood products for use in children and that we use blood products appropriately.

It doesn't take a sophisticated laboratory to make a diagnosis of AIDS. If the epidemiology and the clinical historic patterns are present, we are comfortable in Newark making the diagnosis after simple laboratory studies including: Complete Blood Count (CBC), quantitative immunoglobulin assays, liver function testing, chest X-rays, and HIV antibody testing. Anemia leads the list of abnormalities. These children are almost all anemic and most have elevated liver enzymes.

Table 1. Laboratory Findings in Infants and Children

Hypergammaglobulinemia/Hypogammaglobulinemia	Anemia
Depressed T-helper cells	Leukopenia
Reversed lymphocyte subset ratio	Thrombocytopenia
Depressed lymphocyte responses to mitogens	Elevated level of circulating immune complexes
Decreased specific antibody responses	Elevated serum transaminase levels

The clinical spectrum of illness in children with HIV infection is expanding as our experience with this disease increases. When we looked carefully at our

AIDS and ARC children with failure to thrive, we realized that many of these infants had problems with the central nervous system. Many had a chronic encephalopathy. Others had primary HIV infections of the CNS, with failure to thrive and loss of developmental milestones, the equivalent of the dementia seen in adults. A child who is otherwise well can present with primary CNS infection without any other manifestation of AIDS, and even an essentially normal immune system.

Table 2. Neurologic Findings in Children with HIV Infection

Developmental Delay/Loss of Developmental Milestones	Motor Dysfunction
Chronic Encephalopathy	Microcephaly
Seizure Disorders	Abnormal CT Scan Findings—Cortical Atrophy, Calcifications

One of the clinical problems we have had is dealing with the gastrointestinal manifestations. These children have a variety of GI problems including distension, diarrhea, inability to eat, and tremendous discomfort. The resultant effect is marked malnutrition. In seven of fifteen autopsies, we saw cardiovascular abnormalities. Three were congestive cardiomyopathies and four arteriopathies. One case resulted in a fatal coronary artery aneurysm.

Unlike adults, infants with HIV infection will most likely be symptomatic over the course of their illness. There are some differences between pediatric and adult AIDS, and these are outlined in the following table.

Table 3. Differences between Pediatric and Adult AIDS

1. Kaposi's sarcoma and B cell lymphoma are rare in children
2. Hepatitis B infection is less frequent than in adults
3. Hypergammaglobulinemia is more pronounced in children
4. Peripheral lymphopenia is uncommon in children
5. Lymphoid interstitial pneumonitis (LIP) is much more common in children
6. Some children will have normal ratio of helper to suppressor T cells (although quantitatively T helper cells are diminished)
7. Serious bacterial sepsis is a major problem in children
8. Dysmorphic features may be found in some children
9. Acute mononucleosis-like presentation is rare in children
10. Progressive neurologic disease secondary to primary HIV CNS infection is more pronounced in children

The final mortality rate is unknown, but with our present program at Children's Hospital, we have seen the mortality rate decrease to 35%. With the use of intravenous gamma globulin therapy, the quality of life for our patients has improved, with recurrent septic episodes decreasing from 45% in 1983 to 5% in 1986. We try to provide optimum care to each child, comprehensive rehabilitation services, early intervention programs, and psychological support for the families of our patients. We have learned that HIV probably causes primary infections not only of the immune system, but also of the CNS, heart, kidneys, and liver. This primary multisystem/organ infection with the HIV virus as well as its known secondary opportunistic infections and malignancies present a major problem in devising therapeutic programs. Educational programs regarding the real risk of transmission, i.e., blood contaminated needles used in drug addiction, and sexual contact, need to be extended to school age children and hard-to-reach risk populations. If child-bearing age women at high risk for HIV infection would avoid pregnancy, we eventually would see no new cases of pediatric AIDS.