Human Immunodeficiency Virus And The Fetus

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Abstract: About 2 percent of current cases of acquired immunodeficiency syndrome are among patients less than 13 years of age. When a woman infected by the human immunodeficiency virus (HIV) becomes pregnant, her neonate has approximately a 40 percent chance of becoming infected vertically in the perinatal period. Experience in detecting HIV-infected pregnant women and in diagnosing their affected neonates has been less than satisfactory. In this review, the epidemiology, pathogenesis, transmission, clinical manifestations, diagnosis, and treatment-prevention of perinatal HIV infection are discussed. (J Am Board Fam Pract 1990; 3:181-92.)

“For some patients,” Lockhart has written, “human immunodeficiency virus infection is not acquired, but congenital immunodeficiency.” These patients are babies and children. First described among homosexual men in June 1981, the acquired immunodeficiency syndrome (AIDS) was soon documented among children. Newer evidence suggests the human immunodeficiency virus (HIV) was present as early as 1977 among women intravenous drug users (IVDUs) whose babies later developed pediatric AIDS. As the number of HIV-infected women of childbearing age rose, so did the frequency of infected offspring. In both the United States and third world nations, most AIDS cases among infants and small children have resulted from vertical (mother-to-offspring) transmission of infection during the perinatal* period. Therefore, the demographic features of AIDS in children parallel those of AIDS in women. As providers of care for the mother and the fetus-neonate, family physicians must be knowledgeable about perinatal HIV infection.

Epidemiology
By summer 1989, there were an estimated 500,000 cases of AIDS worldwide, and 5- to 20-million persons were infected with HIV. Participants at a recent workshop convened by the Centers for Disease Control (CDC) concluded that, including patients who have died, the total U.S. HIV prevalence lies between 650,000 and 1.5 million and that by 1993 from 390,000 to 480,000 cases of AIDS will have occurred.

Prevalence of U.S. pediatric AIDS (disease in children less than 13 years old) has ranged between 1 and 2 percent of the total number of cases, although reported cases do not include patients with AIDS-related complex (ARC). As of February 1, 1990, there had been 2055 pediatric AIDS cases reported in the U.S., representing about 1.7 percent of the total. However, AIDS-experienced physicians estimate that only about half of their HIV-infected patients with mild symptoms are included, and all asymptomatic children are still excluded by CDC surveillance criteria. Speculation about the true number of infected children in the U.S. ranges from 2 to 10 for each child who meets official criteria. Between 1988 and 1989, perinatal HIV transmission showed the largest increase among HIV exposure groups (38 percent based upon diagnosed cases). It has been estimated that there are from 1500 to 2000 HIV-infected babies born in the U.S. each year. AIDS is the 9th leading cause of death among children 1 to 4 years old, and, if current trends continue, it will move into the top five causes by 1994. It has been estimated that by 1991 there will be from 10,000 to 20,000 HIV-infected children in the U.S. and that 1 of 10 pediatric hospital beds will be occupied by a child with AIDS.

Data regarding prevalence of HIV infection are incomplete. Estimates depend upon the subgroup tested, and seroprevalence data from...
among women of childbearing age were not reported until fairly recently. General seroprevalence among parturients in Newark, NJ, was 43/1000 (4.3 percent). Among 253,547 women recruits to the U.S. Army, the positivity rate was 0.7/1000. Hypothetically, if these recruits are assumed to be generally representative of our child-bearing population (3.4 million births annually), nearly 2400 HIV-infected women should have given birth in the U.S. in 1988. Anonymous newborn screening surveys are in progress nationwide; a recent serosurvey of all newborns in New York State (276,609 specimens in 13 months) yielded a prevalence figure of 0.66 percent (0.16 percent in upstate New York versus 1.25 percent in New York City).

Geographic Distribution
Most pediatric AIDS cases in the U.S. have been reported from New York, New Jersey, and Florida. Although the geographic distribution of total AIDS cases seems to be shifting away from the mid-Atlantic states (NJ, NY, and PA had 54 percent before 1984 versus 32 percent in 1988), these 3 states retain high rates of IVDU-associated AIDS, and their rates of pediatric AIDS will probably remain relatively high.

The sex distribution of pediatric AIDS cases is roughly equal (54 percent boys, 46 percent girls), but similar to AIDS among women, pediatric AIDS is racially disproportionate (53 percent black, 24 percent white, and 23 percent Hispanic). About 80 percent of children with AIDS in the U.S. have as their only known risk factor for the disease a mother with AIDS or a mother who belongs to a group at high risk for AIDS. Most women with AIDS (78 percent) are of childbearing age.

Risk Factors
The most common risk factors for HIV-infected women in the U.S. remain IVDU (49–52 percent) and, to a lesser degree, heterosexual contact with persons at risk (25–28 percent). In 1988, about 70 percent of perinatally transmitted cases of AIDS were children of mothers who were IVDUs or sex partners of IVDUs. From a number of studies, the rate of HIV infection among regular heterosexual partners of infected persons has been estimated to range from 0 to 58 percent (median 24 percent). Diagnosed cases of AIDS among women and among heterosexual contacts as an HIV exposure group each rose substantially between 1988 and 1989. Data suggest that women IVDUs are a fertile population.

Pathogenesis
HIV (technically, HIV-1) belongs to the lentivirus subfamily of a family of animal viruses referred to as retroviruses because of their characteristic possession of a DNA polymerase termed reverse transcriptase. Recently, HIV-2 has been reported as a cause of AIDS among persons from West and Central Africa, Western Europe, Canada, and Brazil.

Early in AIDS research, it was discovered that HIV demonstrates tropism for the surface glycoprotein receptor (CD4) of thymus-derived helper-inducer lymphocytes (CD4+, T4). It has subsequently been shown that other cell types may be infected by HIV, and these are the key to the transmission of HIV. The hallmark of AIDS is eventual depletion of CD4+ lymphocytes and depression of the normal helper-inducer-to-cytotoxic-suppressor (CD8+, T8) lymphocyte ratio; however, the detailed development of the disease is not understood, and HIV strains apparently differ in their biologic features. The eventual decrease in immune function seems to depend upon various host events in addition to the destruction of CD4+ cells by the virus. Such events include the effects of viral proteins on uninfected cells, viral effects on cytokine production, cytotoxic immune host responses, and autoimmune reactions. For more information about HIV-AIDS pathogenesis, see reviews by Ho and associates and Levy.

Effects on Children
The effect of HIV infection upon the immune systems of children appears to differ somewhat from adults. Early in the course of pediatric AIDS, there is no lymphopenia, and the numbers and function of CD4+ lymphocytes can be maintained for some time, even in the presence of opportunistic infection. Abnormalities of cell-mediated immunity, observed in adults and which are probably related to reduced numbers of T lymphocytes, are not seen early in the course of pediatric AIDS; however, later in its course, most children also have CD4+ depletion,
reversed CD4+/CD8+ ratios, and lymphocyte dysfunction, such as poor mitogenic responses. The most notable early immunodeficiency in children with AIDS is dysfunction of B lymphocytes' antibody production, resulting in recurrent bacterial infections, often including sepsis. This dysfunction paradoxically is accompanied by an early polyclonal hypergammaglobulinemia (but quite possibly associated with hypogammaglobulinemia of IgG subclasses, which can be associated with autoimmune phenomena). Epstein-Barr virus infection can play a role in this polyclonal activation of B cells in AIDS patients.

Transmission
Knowledge about the transmission of HIV is incomplete. Theoretically, the virus can be transmitted from infected mothers to their offspring by three routes:

1. In utero via maternal circulation
2. During parturition by inoculation or ingestion of blood or other infected body fluids (including cervicovaginal secretions)
3. Postnatally by various vectors, possibly including breast milk

More than one route can be involved. The evidence for intrauterine infection includes demonstration of HIV infection of fetal-derived placental tissue, isolation of HIV (or its antigen) from cord blood, the postulated existence of an AIDS fetopathy, isolation of HIV from aborted 15-week and 20-week fetuses, and the fact that delivery by Cesarean section and the postpartum removal of several newborns from maternal care has failed to prevent development of disease in studied babies. More than one route can be involved. The evidence for intrauterine infection includes demonstration of HIV infection of fetal-derived placental tissue, isolation of HIV (or its antigen) from cord blood, the postulated existence of an AIDS fetopathy, isolation of HIV from aborted 15-week and 20-week fetuses, and the fact that delivery by Cesarean section and the postpartum removal of several newborns from maternal care has failed to prevent development of disease in studied babies.

The exact rate of perinatal HIV transmission is not known but can be estimated. Preliminary data support estimates of vertical transmission rates ranging from 20 percent to 65 percent. One study, reported as an abstract, showed that children born to 42 mothers who had previously delivered an infected child had a 50 percent infection rate. The European Collaborative Study, having followed for more than 1 year nearly half of 271 at-risk neonates, reported a 24 percent rate of transmission. Investigators in a multicenter French study evaluated 117 of 308 infants who were 18 months old and born to seropositive mothers. They reported that 27 percent of the babies were seropositive or dead of AIDS and that an additional 8 percent were seronegative but had symptoms suggestive of HIV infection. Current data must be interpreted with caution because many studies have depended upon serologic evidence of infection, which is not completely reliable during infancy. A reasonable average estimate of maternal transmission rate is about 40 percent.

The reported HIV incubation period is from 1 month to 7 years, but it can be longer. The mean incubation for children with transfusion-acquired AIDS is 24 months. Any consideration of postnatal transmission of HIV must include breastfeeding. Transmission by breastfeeding may have occurred, and HIV has been isolated from supposedly cell-free breast milk, yet, instances have been reported of infected mothers who breastfed their infants without apparent transmission of HIV. A recent report from the Soviet Union suggested neonatal-to-maternal transmission of HIV via mothers’ cracked nipples.

Effect of HIV Infection upon Mother and Fetus during Pregnancy
How does HIV infection affect pregnancy? Pregnancy itself is associated with a suppression of cell-mediated immunity: the T cell helper-to-
suppressor ratio is decreased during normal pregnancy, is lowest during the third trimester, and does not return to baseline until as late as 3 months postpartum.\textsuperscript{53} Although progression from asymptomatic HIV infection to symptomatic AIDS during pregnancy is not widely reported, there is some evidence that suggests acceleration of the disease during the gravid state,\textsuperscript{54} and other, newer evidence that militates against such acceleration.\textsuperscript{55,56} Pregnancy might, because of its association with nonspecific symptoms such as fatigue, mask the presence of AIDS-ARC and also delay or modify proposed treatment protocols.\textsuperscript{44}

How does HIV affect the fetus in utero? Ryder, et al.\textsuperscript{41} recently suggested that HIV infection in pregnancy affects newborn health adversely regardless of subsequent documentation of neonatal infection. Their data appear to show that low birth weight, prematurity, and premature death were more common among infants of seropositive mothers and that seropositive mothers with advanced HIV illness were more likely to deliver premature or low-birth-weight babies than asymptomatic seropositive mothers. Conversely, Blanche, et al.\textsuperscript{47} found that neonates later discovered to be HIV-infected did not differ from uninfected infants at birth. Head circumferences, for instance, were identical between the two groups.

**Clinical HIV Disease**

Differentiating AIDS from other congenital infections and primary congenital immunodeficiencies can be quite difficult. Congenital infections with cytomegalovirus (CMV) and Epstein-Barr virus (EBV) can cause immunologic aberrations, and a transient immunodeficiency state (not associated with HIV infection) has been reported among infants born to drug-abusing mothers. However, CMV and EBV immunodeficiencies tend to be more specific and less severe than pediatric AIDS, and the transient syndrome among infants of drug abusers tends to disappear by 18 months of age.\textsuperscript{1}

In several respects, pediatric and adult AIDS are dissimilar. Among infants, AIDS often produces serious bacterial infections and lung disease not seen among adults with the disease. The chronic encephalopathy experienced by children is associated with mental-motor retardation that slows developmental milestones.\textsuperscript{13}

**Recent Classifications**

Acknowledging these differences, the CDC has recently made two modifications in classifying HIV infection among children. The modification reported in April 1987 separates infected children under 15 months of age with perinatal infection from older children with perinatal infection and children with HIV infection acquired through other modes of transmission. Infection is then classified as indeterminate (P-0), asymptomatic (P-1, 3 subclasses), or symptomatic (P-2, 6 subclasses).\textsuperscript{57} In a significant revision of the surveillance case definition for AIDS (August 1987), the CDC focused on the clinical features of AIDS and broadened the application of the definition to children. Recurrent serious bacterial infections and lymphoid interstitial pneumonia (LIP, also known as pulmonary lymphoid hyperplasia) were accepted as indicative of AIDS in HIV-positive children but not adults (Table 1).\textsuperscript{58}

**Clinical Features**

The major clinical features in pediatric AIDS include chronic pneumonitis (LIP — found in about half), recurrent serious bacterial infections and sepsis, persistent or recurrent oral thrush, chronic diarrhea, lymphadenopathy at two or more sites, hepatosplenomegaly, failure to thrive, developmental delay, encephalopathy, microcephaly, smallness for gestational age, thrombocytopenia, parotitis-salivary gland enlargement, opportunistic infections, Kaposi sarcoma, B-cell lymphoma, an eczematoid dermopathy, cardiomyopathy, hepatitis, anemia, nephropathy, asthma, congenital bronchiectasis, clubbing of nails, and seizures.\textsuperscript{1,4,12,31,57,60,61-65} In addition, an AIDS fetopathy-embryopathy syndrome indicative of infection in utero and characterized by such features as a prominent boxlike head, large wide eyes, flattened nasal bridge, blue scleras, and a triangular filtrum has been described,\textsuperscript{37,66} although other investigators have disputed the existence of such a dysmorphic syndrome associated with HIV infection.\textsuperscript{47,67}

The opportunistic infections (OI) in children are very similar to those of adults. *Pneumocystis carinii* is the most frequent cause of infection, especially of pneumonia (PCP).\textsuperscript{68,69} *Candida albicans*, cytomegalovirus (CMV), and herpes simplex virus (HSV) are also frequent opportunistic pathogens. CMV infection, by definition, is an OI only in
Table 1. Summary of August 1987 Revision of Surveillance Case Definition for AIDS.*

I. **Without** laboratory evidence of HIV infection (tests not done or inconclusive†), a patient with AIDS:
   A. Does not have another cause of immunodeficiency, such as the following:
      1. High-dose or long-term systemic corticosteroid therapy or other immunosuppressive-cytotoxic therapy < 3 months before the onset of the indicator disease
      2. Hodgkin disease, non-Hodgkin lymphoma (other than primary brain lymphoma), lymphocytic leukemia, multiple myeloma, other cancer of lymphoreticular-histiocytic tissue, angioimmunoblastic lymphadenopathy < 3 months after diagnosis of the indicator disease
      3. A congenital immunodeficiency syndrome or an acquired immunodeficiency syndrome atypical of HIV infection (such as one with hypogammaglobulinemia)
   and
   B. Has had one of the following AIDS indicator diseases definitively diagnosed:
      1. Candidiasis of the esophagus, trachea, bronchi, or lungs
      2. Extrapulmonary cryptococcosis
      3. Cryptococcosis with diarrhea persisting > 1 month
      4. Cytomegalovirus (CMV) disease of an organ other than liver, spleen, lymph nodes in a patient aged > 1 month
      5. Herpes simplex virus infection causing a mucocutaneous ulcer persisting > 1 month or bronchitis, pneumonitis, or esophagitis in a patient aged > 1 month
      6. Primary lymphoma of the brain in a patient aged < 60 years
      7. Kaposi sarcoma in a patient aged < 60 years
      8. Lymphoid interstitial pneumonia (LIP) in a child aged < 13 years
      9. Mycobacterium avium complex or M. kansasii disease disseminated to site other than lungs, skin, or cervical or hilar lymph nodes
     10. Pneumocystis carinii pneumonia (PCP)
     11. Progressive multifocal leukoencephalopathy
     12. Toxoplasmosis of the brain in a patient aged > 1 month
II. **With** laboratory evidence of HIV infection, a patient with AIDS:
   A. Has one of the already listed AIDS indicator diseases definitively diagnosed or one of the following AIDS indicator diseases definitively diagnosed:
      1. Multiple or recurrent bacterial infections (at least two within 2 years) in a child aged < 13 years, including septicemia, pneumonia, meningoencephalitis, bone or joint infection, abscess of internal organ or body cavity (except otitis media or superficial skin or mucosal abscesses)
      2. Coccidioidomycosis disseminated to a site other than lungs or cervical or hilar lymph nodes
      3. HIV encephalopathy
      4. Histoplasmosis disseminated to a site other than lungs or cervical or hilar lymph nodes
      5. Isosporiasis with diarrhea persisting > 1 month
      6. Kaposi sarcoma
      7. Primary lymphoma of brain
      8. Other non-Hodgkin lymphoma of B-cell or unknown immunologic phenotype
      9. Disseminated nontubercular mycobacterial disease involving a site other than lungs, skin, or cervical or hilar lymph nodes
     10. Tuberculosis involving at least one site other than lungs
     11. Recurrent nontyphoid Salmonella bacteremia
     12. HIV wasting syndrome
   or
   B. One of the following AIDS indicator diseases diagnosed presumptively:
      1. Esophageal candidiasis
      2. CMV retinitis with loss of vision
      3. Kaposi sarcoma
      4. LIP in a child aged < 13 years
      5. Acid-fast infection (species not identified) disseminated to a site other than lungs, skin, or cervical or hilar lymph nodes
     6. PCP
     7. Toxoplasmosis of the brain in a patient aged > 1 month
III. **With** laboratory evidence against HIV infection (negative test results), a patient with AIDS:
   A. Does not have another cause of underlying immunodeficiency (listed in section I above) and
   B. Has had PCP definitively diagnosed or has had definitive diagnosis of one of the AIDS indicator diseases listed in section I above plus a T-helper lymphocyte count < 400/mm³

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*Adapted from MMRW 1987.† Inclues children with seropositivity who are aged < 15 months, have HIV-infected mothers, and do not have other evidence for immunodeficiency or for HIV infection.
children older than 1 month and when located in a site other than liver and lymph nodes; it is often a cause of both pulmonary and disseminated infections in children with pediatric AIDS.\textsuperscript{4} \textit{Candida} is frequently associated with pediatric AIDS as oral thrush (which should not be considered an OI in children less than 1 year of age) and as the cause of sepsis and meningitis, the latter often occurring early in the course of the syndrome.\textsuperscript{1} HSV infections were reported early in the history of pediatric AIDS, and chronic ulcerations caused by this organism seem more frequent in children than adults with AIDS.\textsuperscript{1,31}

\textbf{Bacterial infections} are very common in children with AIDS and often are the first clinical manifestation. Usual anatomic sites are involved, and sepsis is often an accompaniment. \textit{Streptococcus pneumoniae} is the most frequent isolate with sepsis, but gram-negative organisms may be recovered. Staphylococcal skin infections and otitis are frequent, as is \textit{Salmonella} gastroenteritis and sepsis.\textsuperscript{1}

The major cause of morbidity in children with AIDS and ARC is \textit{pulmonary disease}, specifically that secondary to OI (especially PCP) and LIP. LIP is rare in children aged less than 6 years, except in cases of AIDS-ARC. LIP is characterized by a hyperplasia of bronchial lymphoid tissues; also, it is often associated with generalized lymphadenopathy, may not require immediate therapy, and generally carries a better long-term prognosis than PCP. Respiratory distress caused by LIP begins insidiously and is typically unaccompanied by adventitial lung sounds on physical examination unless there is a superimposed bacterial infection.\textsuperscript{1} Respiratory failure in children with AIDS is most commonly due to PCP and CMV pneumonia, but a recent study of 31 patients with pediatric AIDS showed bacteria, especially gram-negative species, as important causes of both primary and superinfections.\textsuperscript{70}

\textit{Failure to thrive} is very common in pediatric AIDS and is not exclusively associated with diarrhea or protein-calorie deficiency.\textsuperscript{4} The postulated AIDS embryopathy and the fact that more than 50 percent of AIDS babies are born gestationally small-sized suggest intrauterine transmission and may indicate a direct inhibitory effect of HIV on growth and development.\textsuperscript{31,41}

\textbf{Developmental abnormalities} are common; delayed motor milestones occur in most children with AIDS-ARC. Psychometric testing can show cognitive dysfunction as well.\textsuperscript{1} HIV has been isolated from the CNS of patients with AIDS and might represent the etiology of these dysfunctions,\textsuperscript{71} although other medical and social factors can be contributory also. Neurological complications in children include encephalopathy, bilateral pyramidal tract signs, rigidity-ataxia, ventricular dilatation, and cerebral atrophy.\textsuperscript{1} For a more complete description of the clinical manifestations of AIDS in children, see Falloon, et al.\textsuperscript{39}

Most children with perinatally transmitted AIDS are recognized by age 2 years.\textsuperscript{48} The average age of onset of symptoms is around 5.5 months, but infected babies can have febrile illnesses in the neonatal period.\textsuperscript{1} Investigators have described a small but growing number of vertically infected children now 6–10 years old, many of whom are clinically well but with evidence of immune dysfunction.\textsuperscript{12}

The exact prognosis in pediatric AIDS is unknown. In general, the outlook for children with ARC is worse than for adults with the same diagnosis,\textsuperscript{1} and the proportion of children known to have died of AIDS is high (estimated at 68 percent), with most deaths occurring within the first 24 months of life.\textsuperscript{20,48} After HIV infection, children seem to become symptomatic sooner than adults; in the multicenter study reported by Blanche, et al.,\textsuperscript{47} 59 percent of HIV-infected infants had severe disease by 18 months of age, whereas among cohorts of asymptomatic seropositive adults, the annual rate of new diagnoses of AIDS has been estimated to be between 2 and 5 percent.

Scott and associates\textsuperscript{72} reported on 172 children with perinatally acquired HIV infection. Their analysis highlighted the concept of the spectrum of clinical aggressiveness of HIV disease. They demonstrated that prognosis depends upon which of the seven common HIV-associated patterns of clinical disease a child presents and at what age the diagnosis is made. The most common first symptomatic manifestation was LIP, which was associated with a median survival of 72 months, whereas children who presented with PCP survived a median time of only 1 month. Previous work has shown that deaths among children aged less than 1 year with pediatric AIDS are significantly higher than among older children; the median survival time for infants has
been estimated at 6.5 months versus 19.7 months for older children. Among the children studied by Scott, et al., the median survival time was 38 months. Children less than 1 year of age at diagnosis survived a median period of only 24.8 months, and the younger the infant when initial symptoms appeared, the less time he or she survived. In addition, there was no plateau in the survival curve from birth, which suggests that no child with perinatally acquired HIV infection will have a normal life expectancy.

Diagnosis
Following the discovery of HIV as the causative agent of AIDS, great effort was expended to develop simple diagnostic tests. At present, several enzyme-linked immunoassay (ELISA) tests are commercially available; they are based upon the reaction of the patient's serum HIV-specific antibodies with a lysate of HIV. Such test results are typically confirmed by a strip radioimmunoassay based upon Western blot methodology, which separates viral proteins by an electrophoretic process, revealing 6 to 9 characteristic bands if antibodies to HIV are present.

One of the most perplexing problems in the study of the vertical transmission of AIDS has been the difficulty in establishing or excluding the diagnosis in neonates and infants unequivocally. Maternal IgG antibodies are transferred to the fetus transplacentally and can persist for up to 15 months. Furthermore, cases of pediatric AIDS have been reported where cultured lymphocytes were positive for HIV, while the patient's blood was seronegative. The loss of antibody to HIV has been reported in children with preterminal AIDS. Therefore, seronegativity does not necessarily exclude congenital HIV infection, and seropositivity in the newborn can be indicative only of maternal infection.

HIV culture is considered to be the most sensitive and specific means of confirming infection; yet, it is technically difficult, time-consuming, expensive, and not widely available. There is also controversy about the amount of blood necessary to assure an adequate number of infected peripheral lymphocytes to confirm infection.

Two newer tests show promise for diagnosis of HIV infection in newborns. The polymerase chain reaction (PCR), a DNA-amplification technique is now commercially available. Rogers, et al. have recently concluded that PCR will be useful both to diagnose accurately neonatal HIV infection and to predict the subsequent development of AIDS. In their report, PCR was quite specific but lacked sensitivity. Slade, et al. have reported on the combination of isoelectric focusing and affinity immunoblotting techniques to identify clonally distinct infant IgG antibodies to HIV; the application of their technique to 10 patients yielded a 100 percent test sensitivity and specificity.

ELISA tests are also being developed that employ recombinant-DNA antigens (especially the p24 antigen) for the screening of sera. This assay requires a relatively large quantity of serum and is limited in its application to newborns because maternal or endogenous anti-p24 antibody often prevents antigen detection, but it may be particularly useful when applied to CSF because the CNS is a major reservoir for HIV. AIDS antigen testing may also be of limited clinical use because of the transience of the "antigen window" before seroconversion.

Treatment and Prevention
Treatment of HIV infection-AIDS can be considered conceptually as: (1) treatment once HIV has already invaded, (2) treatment of the complications of AIDS, and (3) primary prevention of HIV infection.

At the present time, there is no curative treatment protocol for established AIDS. Attempts at "immune reconstruction" with interleukin-2, thymic factors, interferons, or bone marrow transplantation have not been notably successful. A recent trial of continuous intravenous zidovudine (ZDV), also known as azidothymidine (AZT), in children with symptomatic HIV infection showed promise, especially improving symptoms of HIV-related encephalopathy, and the Food and Drug Administration has recently approved an oral formulation of ZDV for treatment of children between the ages of 3 months and 13 years who have symptomatic HIV infection. Clinical trials of other antiretroviral agents, such as ribavirin, didoxycytidine, didoxycyclainosine, didoxyinosine, and soluble CD4 (a protein that inhibits the ability of HIV to infect target cells) are in various stages of planning and completion. In addition, a recent report suggests that ZDV given to HIV-
infected pregnant women may be clinically efficacious and safe for both mother and fetus.\textsuperscript{87}

Treatment of AIDS complications has occupied much clinical energy. Attention has focused upon prevention-treatment of \textit{OI} and reduction of viral replication. The use of periodic intravenous gammaglobulin (IGIV) has been useful in reducing chronic diarrhea and hospitalizations for infection and in enhancing weight gain among HIV-infected children.\textsuperscript{88} IGIV may reduce or eliminate circulating antigens and immune complexes and prevent activation of infected T cells and, hence, reduce (intracellular) viral replication.\textsuperscript{1} Routine use of IGIV in pediatric AIDS remains controversial, however.\textsuperscript{12}

The development of a vaccine against HIV has generated much attention in both lay and scientific communities. Such a vaccine may prove beneficial to women in their childbearing years; however, immunization against HIV presents several serious difficulties (Table 2). Most AIDS investigators agree that if a vaccine is possible, its development is years away.\textsuperscript{85} A British team has recently generated hope for the future with their report of a recombinant-DNA-engineered polio-HIV hybrid virus, which induced effective antibodies in rabbits.\textsuperscript{90}

Because an effective treatment has not been proved, the HIV-infected pregnant woman must

Table 2. Features of HIV Infection That Affect Vaccine Development Adversely.\textsuperscript{*}

- The inherent difficulty of combating an organism whose chief target is a component of the immune system
- Only killing of the infected cell can eliminate the virus because the HIV genome is incorporated into the cell
- Neutralizing antibodies would not affect the cell-to-cell transfer of virus
- The infected cell can remain latent and escape immune recognition
- Vaccination might induce antibodies that enhance HIV infection of cells
- Portions of HIV proteins resemble normal cellular proteins so that immunization might result in autoimmune responses
- Several serotypes and subtypes of HIV exist so that they all may need to be incorporated into a vaccine
- HIV apparently mutates relatively often
- Adequate animal testing of a vaccine is difficult because HIV has not been shown to cause a prolonged AIDS-like illness in any species but man

\textsuperscript{*}Adapted from Falloon, et al.\textsuperscript{99} and Beverley and Sattentau.\textsuperscript{99}

be counseled about the meaning of her seropositivity to herself, her fetus, her spouse-sexual partner, and to her other children. Both parents and their other offspring should be offered antibody testing.\textsuperscript{44}

After counseling, a major focus of caring for the HIV-infected parturient should be the prevention of accidental transmission of the virus. There should be strict adherence to infection control precautions for \textit{all} patients.\textsuperscript{91} Gloves, gogles, and water-repellent gowns should be worn during all deliveries. Oropharyngeal suctioning of neonates should be performed with a bulb device or by modified wall suction rather than with standard oral devices.\textsuperscript{92,93} In the delivery room, neonates should be handled with gloves until blood and amniotic fluid have been removed from the skin\textsuperscript{44}; even in areas where HIV prevalence is low, such precautions are prudent.\textsuperscript{94} Hypodermic needles should not be bent, broken, or resheathed before their discard. A recent study from New York City has shown that needle sticks from patients suspected of being HIV-positive are a significant problem among housestaff caring for children.\textsuperscript{95} Direct contact of the fetus's blood with maternal vaginal secretions should be interdicted when feasible, avoiding, for instance, scalp electrodes and pH sampling when possible.\textsuperscript{44}

In the postpartum period, the infant need not be isolated from the mother.\textsuperscript{44} However, because of the possibility of viral transmission, authorities currently recommend that HIV-infected women in the U.S. and other developed nations not breastfeed.\textsuperscript{7,20,96} Recommendations have been published for the routine immunization of both symptomatic and asymptomatic infants infected with HIV.\textsuperscript{97} There is evidence that immunizations probably do no harm,\textsuperscript{97,98} but there is also evidence that the rate of immunogenicity among HIV-infected patients may be quite low.\textsuperscript{99}

Finally, in the broad sense of treatment, there are the issues of preventing a disease we cannot cure, and of how best to discover those for whom considerations of prevention are too late. Strategy for HIV infection in pregnancy has depended upon antibody testing programs directed toward pregnant women who are willing and able to identify themselves as "at risk." Testing should be performed with the woman's consent after counseling her about the risk factors for
infection and transmission and the likelihood of disease (AIDS and its complications) among women infected with HIV during pregnancy.\textsuperscript{7}

Of special importance about prenatal screening programs for HIV infection are women who are unaware of or deny their high-risk status and those who are infected but asymptomatic. Recently, Imagawa, et al.\textsuperscript{106} documented "silent" infection, whereby nearly 3 years transpired before antibodies could be detected among HIV-infected homosexual men. This raises the possibility of a similarly infected state among pregnant women. Data from pregnant women residing in New York City suggest that only 25–40 percent of those tested for HIV self-identify their high-risk status.\textsuperscript{15,101} As part of a study of 36 HIV-infected children, Pahwa, et al.\textsuperscript{60} reported that only 9 of 20 seropositive mothers were symptomatic. Thus, many infected mothers are ignorant of or reluctant to admit their high-risk status, and many infected women are asymptomatic at the time of delivery.

It has been recommended that all persons seeking treatment for a sexually transmitted disease (STD) and all women of childbearing age with identifiable risks for HIV infection be counseled and tested.\textsuperscript{102} Others, noting the demonstrated poor self-identification and self-reporting of infected women or women at risk, have recommended screening all pregnant women in situations "where there is a combination of high seroprevalence and poor identification of people at risk."\textsuperscript{115, p 270}\textsuperscript{6} Guinan has gone even further and recommended that all sexually active women of childbearing age should be screened and that such screening is more appropriately carried out in the family planning setting than in the obstetrical setting.\textsuperscript{103} General premartial screening appears futile as a means of decreasing perinatal transmission.\textsuperscript{104,105} Most women bearing HIV-infected neonates are unmarried.

The proper frequency of prenatal testing is still in question. It has been recommended that high-risk women be tested before they become pregnant, as soon as they become pregnant, and, if the initial test is negative, again near delivery.\textsuperscript{7}

Studies suggest that the routine use of barrier contraceptives during vaginal intercourse offers significant protective effect against HIV transmission.\textsuperscript{106,107} There is published evidence\textsuperscript{108} and growing concern, however, that condoms do not afford complete protection against HIV transmission.

The presence of other STDs should prompt consideration of a prenatal patient's HIV-status. Persons with gonorrhea or syphilis are more likely to have HIV infection.\textsuperscript{109} In addition, genital ulcerative diseases (i.e., syphilis, herpes, chancroid, and genital warts) multiply the risk of heterosexual HIV transmission.\textsuperscript{109-111}

Finally, partner notification (i.e., contact tracing) still has a definite role in the control of AIDS among heterosexuals. Preliminary reports from states with partner notification programs indicate that from 10–20 percent of sexual partners of HIV-seropositive persons are themselves seropositive. Such programs, therefore, may reach persons who are unaware of their risk for perinatal transmission, especially partners of IVDUs or bisexual men.\textsuperscript{112}

**Conclusion**

HIV infection during pregnancy imposes a cruel, double jeopardy: what is already tragic for the mother can become lethal for the offspring. The fetus-neonate is the passive victim. Although HIV infection in babies and children has been numerically a lightweight, the toll of individual suffering has been a heavy weight, and projections for future caseloads are unsettling.

The medical reality of the day is gloomy; there is much still unknown about the pathogenesis of HIV infection. The very concept "AIDS" is really obsolete\textsuperscript{113}; "HIV infection" more correctly defines the spectrum of the problem. Maternal infection is underdiagnosed, especially because those women with highest likelihood of infection are among the most difficult for health care systems to reach and the most fertile. Neonatal infection is difficult to diagnose because our testing technology, albeit rapidly improving, is relatively unsophisticated.

Prenatal screening for HIV infection has improved, although controversy continues about whom to test. Certainly, in cases where there is any suggestion of symptomatic HIV disease or high-risk behavior, testing should be performed. While the overall proportion of adult heterosexually transmitted cases of AIDS remains less than 5 percent, numbers of cases are increasing; furthermore, HIV infection is increasingly affecting smaller communities.\textsuperscript{14} Thus, if the pre-
dictions of some experts come true, then prenatal HIV screening may become a routine recommendation, as it has for hepatitis B virus.

Today, treatment of both maternal and infant HIV-related morbidity is temporary at best. Amidst research into potentially efficacious intracellular and neonatal therapeutic interventions, the chief current hope of success in helping babies remains to control the spread of HIV infection among women of childbearing age and especially among adolescents. Yet, as Katz and Wilfert have written: “Because current measures of control are necessarily based on behavioral changes involving intravenous drug use and heterosexual practices — changes that are notoriously difficult to achieve — there is little room for optimism about any reduction in the rate of HIV perinatal transmission.”

Nonetheless, for the family physician, who is a health caretaker for both mothers and babies, the quintessential question remains how might we better influence and foster these necessary behavioral changes? The news of AIDS has been odious, but simultaneously, it is opportune. We have an opportunity to educate our patients about the truth of what constitutes healthy behavior. For apart from pathologic maternal behaviors, vertically transmitted HIV infection is nearly totally preventable.

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HIV and the Fetus


