Manifestations of Pediatric AIDS: Proposed Mechanisms of Transmission

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Abstract—Pediatric Acquired Immunodeficiency Syndrome (AIDS) is expected to increase by greater than 75% by 1993. Most of these infants will become infected with the Human Immunodeficiency Virus (HIV) through the mother. It is unclear exactly how the virus is passed from mother to child. The nature of HIV infection is described in this paper, and several mechanisms relevant to its transfer are proposed.

As the number of persons in the US diagnosed with AIDS passes 200 000, (1) an increasing number represent infants infected either 'in utero' or soon after birth. Pediatric AIDS constitutes approximately 1.1% of all AIDS cases; there has been a 46% escalation in pediatric AIDS cases reported since 1989. It is projected that from 1990 to 1993 the number of pediatric AIDS cases will increase by 75–85% (2). Thus, pediatric AIDS exemplifies a medical concern which needs to be addressed separately from a broad spectrum of infectious diseases.

The number of AIDS/HIV infected women of childbearing age worldwide has been estimated as 1 505 000 (3, 4). In the US, women currently represent 11% of all AIDS cases diagnosed in adults. The increase in the number of HIV infected women indicates that a higher percentage of infants will become infected with HIV, since 85% of HIV infected women in the US are between 15 and 44 years of age (2).

Description of HIV

HIV is a retrovirus of the lentivirinae subfamily. These viruses are characterized by a diploid RNA genome, neurotropic behavior, and a long latent period. Infection of the cell begins when the surface glycoprotein (gp 120) of the HIV attaches to the CD4 receptor of the appropriate cell, and the viral glycoprotein gp41 fuses with the cell membrane. The ribonucleic acid is transformed or transcribed into a deoxyribonucleic acid by a viral enzyme known as an RNA-directed DNA polymerase (reverse transcriptase). The transcription occurs within the cytoplasm of the cell, but the transcribed RNA is transferred into the nucleus of a cell, and joined with the host cell’s chromosomes. The virus may become dormant in the cell or may undergo replication. The CD4+ cells which the HIV attacks include T-lymphocytes, primarily the T4 helper cells (T4), cells of the monocyte-macrophage...
lineage, glial cells of the central nervous system, and the chromaffin cells of the gastrointestinal tract. Infection of the chromaffin and glial cell may result in severe diarrhea and neuropathy which often accompanies HIV infection. The primary role of the CD4+ T helper cell in immunity is to stimulate immunoglobulin secretion by B-lymphocytes, and to induce other classes of T-cells to proliferate. Normal levels range from 1000–1500 CD4+ cells per cubic millimeter, while in patients diagnosed with AIDS, levels drop below 200 (5). This loss of T-helper cells results in a profound immunodeficiency.

**HIV infection among adult women**

Women are primarily infected by HIV through one of three major transmission routes: 1) intravenous drug use 2) through sexual intercourse with an intravenous drug user, or, in previous years, 3) blood transfusions. IV drug abuse is currently the major route by which women become infected (51% of HIV infected women). 33% of HIV infected women have acquired the virus via heterosexual contact. Of these women, 62% were infected through sexual encounters with IV drug users and 10% through sexual encounters with a bisexual male (Table 1). In most cases one or both of the partners had microscopic lesions which allowed HIV to enter through the epidermis via sperm or other genital and epidermal secretions.

**Risk behavior among HIV positive women**

58% of HIV infected females are Black, while 21% are Caucasian and 20% are Hispanic females. Of the women infected through sexual intercourse, 49% are Black, 31% are Hispanic, and 20% are Caucasian (1). It has been suggested that the higher number of HIV cases in minorities is in part a function of their lower socio-economic level. The ability to purchase contraceptive devices is often limited among women of minority groups because of their lower income (6). Female intravenous drug users often do not use contraceptive methods effectively. The use of heroin may eliminate or minimize the menses of the endometrium. Therefore, when female IV drug abusers recognize that their menses' flow is eliminated, they may assume that they have become infertile. When engaging in heterosexual activity, women who carry out these risk behaviors may not use spermicidal jellies or creams (or inform their partner to use a condom, for a variety of reasons) because they assess that they are unable to conceive children. In many instances, the partner simply refuses to use a condom. Thus, the risk of infecting a child which has been conceived increases. Historically, the major contraception method used by female IV drug abusers has been the 'pill' (7) which needs to be taken consecutively to serve as an effective deterrent against fertilization. However, the drug user may be disoriented because of her drug abuse; she may discontinue the pill medication. When she engages in sexual intercourse with an HIV carrier, fertilization is more likely to occur, and the probability of HIV infection of the fetus also increases.

**Expression of pediatric AIDS**

Pediatric AIDS is defined as a diagnosis in children less than 13 years of age. Between 1980 and April

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**Table 1 Female exposure to HIV/human immunodeficiency syndrome**

<table>
<thead>
<tr>
<th>Exposure class</th>
<th>Number of women HIV-infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Drug Abuse</td>
<td>8537 (51%)</td>
</tr>
<tr>
<td>Sexual contact</td>
<td>5534 (33%)</td>
</tr>
<tr>
<td>- Sexual intercourse with IV drug abuser</td>
<td>3451 (62%)</td>
</tr>
<tr>
<td>- Sexual intercourse with an HIV-infected person</td>
<td>698 (13%)</td>
</tr>
<tr>
<td>- Sexual intercourse with a bisexual male</td>
<td>540 (10%)</td>
</tr>
<tr>
<td>Blood transfusion recipient</td>
<td>1496 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>1238 (7%)</td>
</tr>
</tbody>
</table>

a. Women are between 15 and 44 years of age. b. Other means of HIV infection via sexual intercourse are specified in the text. c. Blood transfusion is a means by which HIV is transferred through epidermal contact with the blood of an HIV-infected person or through a clinical transfusion. d. The term 'other' implies patients who refused to submit to questioning about their HIV-positive condition, who died, and who were not pursued for further information about their condition. * Adapted from Centers for Disease Control. HIV/AIDS Surveillance Report, April 1991; p 10.
MANIFESTATIONS OF PEDIATRIC AIDS

1991, 2963 pediatric AIDS cases have been reported, with 2411 of these cases occurring in infants below the age of 5. 54% of the HIV infected pediatric infants were male, while 46% of HIV infected pediatric infants were female. Black infants represent over half of pediatric AIDS cases, and Caucasian infants represent most of the remainder (Table 2).

As indicated above, infants may be indirectly infected as a result of the mother’s risk behavior, (Table 1). Infants who are born to HIV-positive, drug-abusing mothers generally are classified in the P-1 group and usually develop immune abnormalities in early postpartum (Table 3). Exposing the fetus to intravenous drugs may drop the lymphocyte count by as much as 46% below that normally found immediately after birth (9); life expectancy decreases because the immune system is less likely to resist infection. Although, at birth, HIV-negative infants possess higher numbers of T4-helper cells than adults (5), the T-4 helper cells in an IV drug exposed infant decrease by 30% when compared with a drug-free infant (8). One could suggest that the infant’s exposure to drugs such as methadone and heroin minimizes the effectiveness of the immune system, and if HIV infection occurs, the incubation period for HIV is drastically shortened (9). Infants placed in the class P-O may not be infected by HIV, but they possess antibody directed against HIV, acquired through the transfer of the maternal immunoglobulin (IgG) across the placental membrane (10).

Class P-1 infants are infected with HIV, but they do not yet express P-2 symptoms of immunodeficiency. Nevertheless, the infant may express immunological abnormalities; increased levels of IgG are common. Although it is highly probable that the infant’s lymphatic system is responding to HIV infection, the high levels of antibodies may be induced by other infectious agents, or even result from the eruption of the deciduous teeth. Immune abnormalities may also be manifested as a decreased ratio of the lymphocytes of T4 helper cells to T8 cytotoxic/suppressor cells (10, 11).

Infants classed as P-2 express symptoms of HIV infections as defined below.

Subclass A infants express persistent fever, failure-to-thrive, and a loss of 10% or more of the infant’s weight (13). The weight loss may be caused by recurrent or persistent diarrhea, or by the lack of appetite which often accompanies a fever. Hepatomegaly, splenomegaly, and lymphadenopathy also indicate unexplained manifestations of the HIV infection.

Subclass B infants express a neurological decline in the developmental plateaus: blinking, facial gestures, and verbal behavior. Abnormal ocular movements may be an earlier indication of HIV infection in P-O and P-1 infants because the central nervous system is infected before immunodeficiency occurs (12). Exactly why this is the case is not known. One may conjecture that because the (IV) trochlear nerve is the thinnest of the 12 cranial nerves, it may be infected the earliest, and thereby become inoperative sooner than the other cranial nerves. Thus, impulses from the trochlear nerve to the superior oblique extrinsic ocular muscle may not induce the muscle to rotate and the infected infant ceases to rotate the eyeball in a downward lateral motion. Loss of head movement and a change in tone may indicate the deterioration of

Table 2 Pediatric AIDS cases categorized by racial ethnic orientation*

<table>
<thead>
<tr>
<th></th>
<th>Caucasian non-Hispanic</th>
<th>Black non-Hispanic</th>
<th>Hispanic</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia-coagulation disorder</td>
<td>100(68%)</td>
<td>19(13%)</td>
<td>24(16%)</td>
<td>3(2%)</td>
</tr>
<tr>
<td>Parent at risk for HIV infection</td>
<td>391(16%)</td>
<td>1434</td>
<td>642(26%)</td>
<td>15(—)</td>
</tr>
<tr>
<td>- intravenous drug abuse</td>
<td>189</td>
<td>703</td>
<td>328</td>
<td>4</td>
</tr>
<tr>
<td>- sex with drug abuser</td>
<td>80</td>
<td>231</td>
<td>203</td>
<td>3</td>
</tr>
<tr>
<td>Received blood transfusion</td>
<td>139</td>
<td>55</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>132</td>
<td>538</td>
<td>131</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 3 Classification of human immunodeficiency virus (HIV) pediatric cases*

<table>
<thead>
<tr>
<th>Class P-0. Indeterminate Infections</th>
<th>The presence of HIV antibody in the infant's bloodstream is the only indication of possible HIV infection.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class P-1. Unexplained HIV Infections</td>
<td>Subclass A: The infant does not express immune abnormalities even though its mother possessed HIV. Subclass B: Immune abnormalities occur: hypergammaglobulinemia, decreased T-helper/T-suppressor cell ratio, and absolute lymphopenia. Subclass C: Infants may have been tested for Subclass B symptoms, but further testing was discontinued because the infant may not have been brought back to clinic for further testing.</td>
</tr>
<tr>
<td>Class P-2. Clinical Manifestations of HIV Infections</td>
<td>Infants, who are diagnosed with physical symptoms caused by HIV, possess primarily Subclass P-0 in Infants. Subclass A: General physical signs for HIV infection. Children persist with a fever, failure-to-thrive, weight loss, hepatomegaly, splenomegaly, and lymphadenopathy in which the lymph nodes increase in width to 0.5 cm or more. Subclass B: Neurological associated disorders with HIV. Motor control deteriorates, manifested through paresis, deeper or higher vocal tone, ataxia, and gait disturbance. Subclass C: Lymphoid interstitial pneumonitis (LIP). LIP consists of extensive infiltration of the lungs with mononuclear cells. Pathogens are dismissed as possible causes of LIP. Chronic bilateral reticulonodular infiltrates are visible from X-rays, and the presence of the infiltrates continues for 2 months or more. Subclass D: Infections directly linked to immunodeficiency. Category D-1: Patients suffer from a variety of opportunistic infectious disease which have been reported to the CDC. Category D-2: Infants have recurrent bacterial infections. Category D-3: Infants are infected with the dermal diseases such as oral candidiasis, herpes stomatitis, and herpes zoster. Subclass E: HIV associated cancers. Category E-1: Infants are diagnosed with secondary cancers such as Kaposi's sarcoma, B-cell non-Hodgkin's lymphoma, and neurological lymphoma. Category E-2: Other cancers which occur as a secondary means to the HIV infection. Subclass F: Other manifestations. Other manifestations which occur may or may not be directly correlated with HIV infection in infants. The CDC does not currently place these symptoms into categories, (hepatitis, cardiopathy, etc).</td>
</tr>
</tbody>
</table>


the accessory (XI) nerve by HIV. Paresis, abnormal tone, ataxia, and gait disturbance are also common symptoms induced neurological deterioration. Subclass C infants suffer from Lymphoid Interstitial Pneumocystis (LIP). LIP is manifested as an upper respiratory infection, resulting in diffusion of lymphocytes and plasma cells through the bronchial lymphoid tissue. LIP occurs in approximately 40% of all HIV infected children, and is not known to be associated with parasitic infection (14). The syndrome is often accompanied by parotid enlargement, and elevated levels of immunoglobins. The Mediastinal nodes may also become enlarged.

Subclass D infants are diagnosed with infectious diseases as a direct result of HIV induced immunodeficiency. Category D-1 infants may develop a variety of syndromes, including Pneumocystis carinii pneumonia (PCP), chronic cryptosporidiosis, toxoplasmosis, chronic isoporiasis, esophageal, bronchial, or pulmonary candidiasis and cytomegalovirus infections. Chronic herpetic simplex may infect the cutaneous layer of the mucous membranes of the buccal cavity. Nocardiosis, chronic leukoencephalopathy, and other opportunistic infections have also been reported by the CDC (10). PCP occurs in approximately 70% of all HIV infected infants; approximately 64%

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of the infants who are diagnosed with acute PCP die from the infection (5).

In an HIV infected adult, a CD4+ cell count above 250 cells per cubic millimeter indicates that PCP has a 0.06% probability of occurrence. However, in HIV infected infants, there is a 6% chance that PCP may develop when the CD4+ cell count is above 250 (15). The CD4+ cell count may be higher in infants than in adults because there is an increase in T-lymphocytes production immediately after parturition. Within the first year, a clinically healthy infant's CD4+ count is approximately 3500 cells per cubic millimeter, but it regresses to the range of 1500 and 2000 T-lymphocytes by the age of two (5, 16). Because the infant is more susceptible to infection immediately after birth, the cortical cells of the thymus may induce an escalated development of immature stem cells, resulting in an increase in T-lymphocytes (17). The increase in T-lymphocytes may also be caused by excessive secretions of thymopoietin. Some of the 90% of immature T-lymphocytes or lymphoblasts which usually degenerate may be biochemically stimulated to mature and become functional by exposure to the thymopoietin, increasing the number of T-lymphocytes in circulation.

Category D-2 represents infants who have developed recurrent bacterial infections, including meningitis, pneumonia, bone and joint infections. Category D-3 includes infants developing persistent and recurrent dermal infections such as oral candidiasis, herpes zoster, and herpes stomatitis. The most common symptom of this category is oral candidiasis. The mould Candida albicans causes fungal colonies which macroscopically appear as white and creamy lesions on the stratified squamous epithelium in the buccal cavity (18).

Subclass E includes infants who have developed secondary cancers such as Kaposi's sarcoma, primary lymphoma, and B-cell non-Hodgkin's lymphoma.

Subclass F includes infants who develop nonclinical manifestations of the HIV. Thus, these conditions may also be correlated with other physical abnormalities besides HIV infection such as hepatitis, cardiopathy, nephropathy, and anemia (10) (Table 2)

Detection of HIV

It is difficult to diagnose HIV in infants immediately after parturition, because the current HIV tests (ELISA, Western Blot) deduce an infective state through detections of increased level of immunoglobin G(IgG). The maternal immunoglobin remains in the infants' bloodstream between 28–38 days. Thus, it is indicative that the infant has been HIV infected only when the immunoglobulin G levels persist for 15 months or more (19).

Two additional methods may be used to detect HIV infection prior to the onset of clinical symptoms: the Polymerase Chain Reaction (PCR) and the antibody binding test. The PCR test detects HIV by amplifying the proviral DNA sequence from mononuclear cells in the bloodstream. As a result of PCR test, a single HIV DNA molecule present in 100 000–150 000 mononuclear cells, can be detected. From 30–50% of the infants who are born to HIV infected women become infected with HIV. Therefore, the PCR test may predict the presence of HIV in the bloodstream before immune abnormalities and/or increased levels of immunoglobulin signify probable HIV infection (20). This test has detected HIV DNA over 3 months before immunodeficiency was expressed. Therefore, (at least in theory) medication may be administered prior to development of infectious diseases, and the immune system is strengthened in its resistance to HIV infection (20,21).

The antibody binding test uses the ELISA technique to detect immunoglobin directed against the principal neutralizing domain (PND) of HIV strains. Absorbance levels of maternal immunoglobulin decreased as the concentration of the PND decreased. High affinity antibody is indicated by increased band intensity in the assay; low affinity antibody results in a band of lesser intensity. The affinity of antibody directed against the PND may therefore correlate with progression of the disease (22).

The ratio of T4 helper cells to T8 cytolytic/suppressor cells is itself indicative of the extent of immunosuppression. A normal T4/T8 ratio in infants older than 6 months, and also in adults, is in the range of 1.2–2.6. Therefore, T4/T8 ratios below 1.2 are considered abnormal. Further testing of the ratio is often performed for infants below the age of 6 months. However, HIV infected infants below the age of 6 months have expressed T4/T8 ratios as low as 0.4 in the absence of obvious immunosuppression (18) (Personal Communication, Dr Philip A Pizzo). Infants who develop immunodeficiency sequelae such as PCP, persistent diarrhea, Kaposi's sarcoma, or other infectious ailments as specified by the Center for Disease Control, are diagnosed as suffering from AIDS (10).

Mechanisms of HIV infection in infants

Several periods both prenatally and postnatally lend themselves to possible mechanism of HIV infection. These mechanisms include 1) cross placental infection, 2) exposure during parturition, and 3) exposure to fluids of the mother, primarily colostrum. Approx-
imately 80% of HIV infected children acquired their condition transplacently or perinatally (Personal Communication, Dr Philip A Pizzo). After 4 months of fetal development, the surface area of the placenta increases to compensate for the larger fetus. However, the placental barrier becomes thinner, because there is no increase in tissue from the uterine wall of the mother. Therefore, the infant's bloodstream may become more accessible to the virus, and the virus can infect the appropriate cells. HIV is probably transmitted transplacently via CD4+ receptor containing placental tissues: chorionic villi, the cytoplasmic cells in the stroma of the cytotrophoblast, or via the peripheral surface of the endothelial lining of the arterioles and capillaries (23). However, it has also been proposed, that if viral propagation is rapidly being carried out, that permeability of the placenta may increase (24). The precise mechanism by which the HIV is transmitted is uncertain. HIV can infect the placental tissue as early as the 15th or 20th week into gestation, because the placental tissues become fully developed by the end of the first trimester (23).

The likelihood of infection may also vary with the stage of gestation. During the first trimester of development, surface layers of the fetus are undergoing formation; target cells may be more accessible in the first 5 months of gestation as compared with the last 4 months of gestation. The four layers of the dermis (stratum corneum, stratum granulosum, stratum lucidum, and stratum germinavatum) have formed by the 6th month. Therefore, the probability of HIV to enter via the skin is minimized during the last 4 months of gestation. Nevertheless, the fetus' stratum corneum is still thinner than that of the adult's (25). As a result, the remaining tissues of the periderm and secretions from the sebaceous glands form a dense and viscous protective covering known as the vernix caseosa. The vernix caseosa provides a temporary extra layer to the epidermis, minimizing chances of infection through the skin in the later stages of gestation.

As the fetus is expelled from the uterus and enters the vagina before expulsion, the infant's buccal cavity becomes full of amniotic fluid and maternal blood both from cervical and vaginal secretions, and from tearing of tissues. Both of these fluids can contain HIV (26). Once the infant has been expelled from the uterus, it will attempt to ventilate its lungs; the infant will try to swallow. The constrictor muscles of the pharynx contract and the HIV containing fluid enters the esophagus, which contains CD4+ cells (27); infection may occur. Although there have not been documented cases of HIV infection via the esophagus, the presence of Langerhans cells in the esophageal tissue may increase the likelihood of HIV infection (28). Within the skin, Langerhans cells serve a lymphoid function, primarily as antigen presenting dendritic cells. Like the T-helper cells, they also express the CD4+ receptor (26). The mould, Candida, is known to enter the bloodstream via oral lesions; HIV may also directly enter the bloodstream through oral lesions (27). The infant's swallowing of amniotic fluid during gestation may also theoretically be a route for HIV infection in the buccal cavity, esophagus, and in the stomach.

Since nursing of the infant is a means of fluid transfer from the mother, several instances of infection of the newborn have resulted from breast feeding on the part of the infected mother. HTLV is thought to be transferred in the milk through infected T-cells (29); it is uncertain whether HIV can be transferred to the infant by free virus within the milk (30). Nor is the mechanism clear by which the virus actually penetrates the subject. The nature of conditions within the mouth may play a role. For example, the central incisors of the infant pierce through upper squamous epithelium approximately 6–8 months after birth. Lateral incisors arise 8–10 months after birth. The upper layer of skin in the infant is only 0.01–0.05mm thick, while in the adult, the stratum corneum of the adult has a thickness between 0.1–0.9mm (25). It is likely that the infant's skin in the buccal cavity is also thinner than in an adult. Therefore, the infant's skin may not function effectively as a protective shield from the virus.

Langerhans cells are heavily concentrated within the fissures between the infant's deciduous teeth (17). In infants, epithelial cells encroach on the enamel of the infant's tooth. Thus, the Langerhans cells are closer to the upper surface of the mouth, and they would have a greater probability to be infected by HIV. When the mother's fluids in the form of infected colostrum or milk contact the buccal region, HIV infection may occur.

The infant can also be infected with the HIV as a result of direct contact with the mother's nipple and areola during nursing. Since the peripheral and the internal region of the areola is supplied with lymphatic vessels, biting at the nipple and areola by the infant may result in the bursting of the lymph vessels. Lymph which contains infected T-helper cells and other appropriate cells may contact and infect the infant's epithelium. Furthermore, the continuous sucking of the infant causes stretching of the areola, which in turn leads to cracking of the tissue (31).
The maternal alveolar cells are the cells which secrete the colostrum and the milk from the available fluids in the bloodstream. As the maternal infectious condition intensifies, the number of HIV particles also increases in the bloodstream. There is a greater likelihood that the number of viruses that infiltrate into the colostrum and into the milk increases (4).

Lymph vessels are also located in the walls of the lactiferous ducts. Thus, when the milk flows through the lactiferous ducts, the lactiferous duct may become distended. This may lead to microscopic rupturing of the lymphatic vessels, and infected cells become miscible with the milk. The HIV within the milk is transferred into the buccal cavity of the infant where it can attack the appropriate cells.

The infant's stomach immediately after birth has a pH similar to that of the bloodstream, pH 7.4. When the infant begins to ingest milk and other forms of nutrition, oxytotic cells begin to secrete hydrochloric acid. The pH in the stomach decreases to a pH between 4 and 5, but it is a gradual process, and the pH would not be immediately low enough to inactivate the virus. As a result, the HIV could infect Langerhans cells of the stomach (27), or the virus could spread into the duodenum, colon or rectum, all of which contain chromaffin cells which can be infected by the HIV. If the HIV reaches the anal column, it could be in the faecal matter or in a liquified form.

The HIV is more likely to enter the glands in the anal sinuses, the external surfaces of which possess lymphocytes (32).

It is also plausible that the absorptive epithelial or chromaffin cells of the duodenum and colon become infected, and become lost from the peripheral surface of the intestinal mucosa. As a result, crypts arise and by active transport. However, when the absorbing chromaffin cells are sloughed off from the immature crypt cells, the bile acids are hindered from transport to the hepatic portal vein. Because infected infants have high levels of bile salts in their stool, one may hypothesize that the HIV affects the chromaffin cells of the distal ilium or small intestine where bile acid absorption primarily occurs (33-35).

As the number of women infected with HIV increases physicians will be confronted with more pediatric AIDS cases. Since there is no medication to completely eliminate the results of HIV infection, an awareness of the means by which the virus is transferred to the fetus and/or to the infant, and the extent of the virus in women, would obviously lead to a better means of prevention.

References


