

**Vertical Transmission  
of  
Human Immunodeficiency Virus**

by  
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Transmission of HIV, human immunodeficiency virus, can occur through various mechanisms. Sexual intercourse, intravenous drug use, and blood transfusions are some of the better known paths. The least understood and most complex mode, however, is vertical transmission. Vertical transmission is the transmission of HIV from mother to infant. The possible mechanisms through which this occurs are currently under intense study. Understanding the time and place HIV transmission occurs is of crucial importance in developing a possible cure or prevention. Although little is known, it is thought that this form of transmission may be the easiest to prevent. The magnitude of pediatric HIV infection world wide is alarming. It is, of course, directly related to the increase of infection in the adult population, primarily women of reproductive age. This paper will examine HIV, those pathways of transmission that are under acute investigation, and the future implications as well as the present situation as they relate to pediatric infection and the overall pediatric population.

Human immunodeficiency virus is a member of the ribonucleic acid (RNA) containing retrovirus family. Being a retrovirus, HIV has the unique ability to synthesize a deoxyribonucleic acid (DNA) copy of itself using an enzyme called reverse transcriptase. The virion is composed of a single stranded, linear RNA nuclear core containing 3 important genes gag, pol, and env. The gag gene codes for the inner core proteins while the pol gene codes for the enzyme reverse transcriptase which is present within the virion (1). It is this enzyme that is used to synthesize a DNA copy, called provirus DNA, from the viral RNA which can then integrate itself into the host cell's genome. A lipid envelope surrounds the viral components. This envelope, encoded by the gene env, is highly variable and accounts, in a large way, for why the virus is so difficult for the immune system to control.

Specifically, the virion affects those cells that play a role in the immune system, T cells, B cells, monocytes, and macrophage. Any cell exhibiting a CD4 molecule on its cell membrane has an affinity for the HIV envelope. Attachment of the virion to the CD4 receptor site leads to the fusion and then penetration of the virion's nucleocapsid (nucleic

acid-protein shell) into the attached cell. Following infection, the viral genome begins its synthesis phase. During this phase the virus constructs a viral DNA strand from its original RNA genome through the use of its reverse transcriptase. After synthesis the provirus DNA becomes incorporated into the DNA of the cell from which all future viral proteins will be translated or new virus will be produced (2). Integration of the provirus DNA into the normal cellular DNA can cause continuous low or high level reproduction of viral infected daughter cells. Depending upon the activity or nature of the infected cell, the pro-virus can lie dormant for some period of time. This ability to lie dormant or establish viral persistence accounts for the few weeks to ten year time frame that is observed in developing symptoms of Acquired Immune Deficiency Syndrome (AIDS), a disease caused by HIV.

The main immunologic effect of HIV infection is the depletion of T4 cells through direct and indirect cytopathic mechanisms. Infection of the T4 lymphocyte is a critical moment in the pathogenicity of the virus. The T4 lymphocyte essentially coordinates a person's immune response to foreign agents. Infection of T4 cells by HIV can lead to cell fusion of the infected cells with surrounding noninfected T4 cells and eventual death of these large multi-nucleated cells (syncytia) (1). The extraordinary loss of T4 cells during AIDS cannot be easily explained, however, by simple virus induced depletion by syncytia. The exact role HIV plays in the death of these cells is still unclear and is the subject of intense study. Nonetheless, loss of the T4 cell is significant. The T4 cell is responsible for the activation of macrophage, cytotoxic T cells, and B cells, all of which play a role in isolating and neutralizing viral infiltrators (1). The loss of the T4 cell is basically a loss in the ability of the human body to mount an effective immune response to a foreign agent.

In the case of the pediatric population, especially neonates, this becomes increasingly important. As adults the immune system has matured and steadily developed having an immune memory based on long-lived lymphocytes to a wide range of antigens. However, in neonates, the immune system is very immature and underdeveloped.

Therefore most of a neonate's immunity comes passively through antibodies from its mother. Through these antibodies, specifically immunoglobulin G (IgG), protection is passed via the placenta from mother to fetus (3). A neonate's immunity lies in just the type of antibodies passed from its mother which have a finite life span in the neonate and then disappear. Also, the quantity of T cells in a neonate is relatively small compared to that of an adult although HIV's effect on the T-cell population is essentially the same for both an adult and the child.

In a study to determine immunologic effects of HIV on children and their significance in determining clinical outcome, Martino et al examined 675 children born to HIV infected mothers. Neutrophil, lymphocyte and T-cell subset (CD4+, CD8+) numbers and immunoglobulin levels were evaluated over a period spanning from birth to two years of age. The children were categorized into three groups; P1 (infected children exhibiting no symptoms), P2 (infected children with symptoms) and noninfected children. Martino et al found that overall, at any given age in either group, total neutrophil and lymphocyte numbers did not differ. However, CD4+ cell counts of P2 children, at any given age, were significantly lower than P1 or uninfected children. CD8+ cell counts of P2 children, at any given age, were also higher than either P1 or uninfected children. In the early stages (1 - 6 months) both P1 and uninfected children cell counts were consistently the same. Only in the latter stages (13 - 24 months) was there observed a difference in both CD4+ and CD8+ cell counts between P1 and uninfected children. At that time, some of the P1 children were exhibiting symptoms of infection. The display of symptoms along with decreasing numbers of CD4+ lymphocytes and increasing numbers of CD8+ lymphocytes indicates, according to Martino et al, that the immunologic deviations are indicative of a clinical outcome rather than infection status. In addition, CD4+ lymphocyte fluctuations as well as immunoglobulin levels have been shown to correlate with the degree of symptoms both in adults as well as children (4).

As of January 1992, the Centers for Disease Control (CDC) reported 3471 AIDS

cases in the United States pediatric population. Pediatric is defined as 12 years old or younger. This accounts for 2% of the total reported AIDS cases within the U.S. This figure however, does not include those children having HIV infection but not diagnosed as having AIDS. Of these 3471 cases, 2936 were a result of exposure to a mother who was at risk for HIV infection (5). This means that 85% of the children reported to have AIDS were infected by their mother. This is in contrast to the 8% attributed to blood transfusions, the 5% attributed to hemophilia disorders and 2% which are undetermined (5). This demonstrates that vertical transmission, transmission from mother to infant, is a primary pathway for pediatric HIV infection.

Current rates of vertical transmission of HIV have been based on a multitude of studies conducted worldwide. In a New York study a transmission rate of 29% was determined (6). In the Italian Multicentre Study a rate of 33% was found and a separate French study calculated a transmission rate of 27% (7, 8). A rate as high as 45% was reported in a study conducted in Nairobi Kenya (13). However, the European Collaborative Study refutes transmission rates as high as those previously reported and reports a transmission rate of 13% (9).

The European Collaborative Study examined 600 children born to HIV infected mothers. Of those 600, 372 children's infection status was known and 48 (13%) of those 372 were found to be infected. Infection status was determined at regular intervals in each of the 372 children. Testing was conducted beyond the age of 18 months. Infection was determined to be the presence of antibody. However, when antibody was no longer detected and seroconversion was assumed to have occurred, isolation of the virus was attempted. In 10 of 163 children in which viral isolation was attempted a positive result for infection was obtained. According to the European Collaborative Study group, the fault of the previously reported transmission rates was a lack of specificity and definition of infection (9). This was not the case in the Italian Multicentre Study.

In the Italian Multicentre Study, all children born to seropositive mothers were reported and infection was determined to be the presence of antibody at 18 months. Loss

of antibody was followed up with viral detection via Polymerase Chain Reaction method and still 32 of 128 children were found to be HIV positive (25%). In the study 9 children failed to be checked up at 18 months and 2 died suddenly before 18 months of age. These 11 assumed to be HIV infected, added to the 32 already known infected, gives a total of 43 children infected or a transmission rate of 33% (7). Both the European Collaborative Study and the Italian Multicentre Study were very extensive and specific and both have obtained drastically different transmission rates. This shows the complexity and difficulty in determining the actual rate of transmission. Factors such as human error, loss of subjects, and the difficulty in determining infection through current detection methods can alter the calculated transmission rates. This leaves us with calculated rates ranging from 13% to 45%, with the true rate we can be sure lying somewhere in between.

The effect of HIV infection on a newborn is both rapid and devastating. During a time span of three years, January 1988 thru December 1991, a total of 221 pediatric AIDS cases were reported in the U.S. (5). During that same time interval, 1192, or 54% of those cases ended in the death of the individual (5). Overall 1850 deaths have occurred (5). According to the CDC, the top three pediatric AIDS-indicator diseases observed are *Pneumocystis carinii* pneumonia accounting for 25% of the cases reported, multiple or recurrent bacterial infections, 18%, and HIV encephalopathy (dementia), 14% (5). Other diseases indicating AIDS, such as HIV wasting syndrome and lymphoid interstitial pneumonia are also common. Although effects of HIV infection may not appear for as many as 10 years in adults, it is observed that in pediatric cases the effects appear much sooner, as early as a few months. It is reported that 35% of the children reported to have been infected with HIV perinatally who developed *Pneumocystis carinii* pneumonia died within two months of their diagnosis (10). Once AIDS has been diagnosed the child succumbs much more quickly to the disease due to their severely damaged and inadequate immune system.

Determining how and when perinatal HIV transmission occurs will increase our chances of success in developing a strategy to prevent or interrupt vertical transmission.

Currently vertical transmission has been demonstrated to occur at 3 different time frames, during pregnancy, intrapartum and postpartum.

Vertical transmission during pregnancy is a poorly understood mechanism and almost nothing is known about how it occurs, although it is known to occur. HIV infection has been demonstrated in fetuses after 8-15 weeks of gestation (10). Sampling of amniotic fluid is a technique currently being used to determine the presence of infection *in utero*. One study has shown HIV to be present in early fetal tissue, the trophoblastic cells. These cells form a layer early in embryonic life that lie in proximity to the point at which exchange takes place between the mother's and fetus' circulatory systems. Early fetal blood precursor cells have also been found to contain HIV (11). No concrete evidence, however, has been obtained showing the exact point in time or place where the maternal virus is transmitted unto the fetus.

A second period when HIV infection is known to occur is the intrapartum period, the period of time encompassing delivery. It is hypothesized that this is the most common pathway of transmission. During this time, there is the opportunity for the newborn's gastrointestinal tract to come into contact with the infectious maternal blood and other secretions associated with the birth canal. Although no concrete evidence has appeared to show the benefit of cesarean delivery over natural childbirth, there have been studies that have demonstrated the effects of natural childbirth on transmission. One study in particular has acquired some interesting data. Dr. James J. Goedert and his associates performed a study on twins to determine the transmission rate for each of the twins. Their study consisted of 100 sets of twins from nine different countries, born to HIV infected mothers. Their findings showed that the risk of transmission was definitely higher for the first-born twin than the second-born twin. The risk of transmission for the first-born when delivery was vaginal was determined to be 50% while the risk of transmission for the second-born was a mere 19%. Cesarean deliveries for the first-born were determined to have a risk of 38%, still higher than the 19% calculated for the second-born twin delivered cesarean (12). These findings suggest that exposure of the first-born twin to

maternal blood and secretions associated with the birth canal is a viable and substantial means of transmitting HIV infection from mother to infant, both through natural childbirth and cesarean delivery. According to Goedert, the lower percentage transmission in the second-born twin through vaginal delivery can be attributed to the cleansing of the birth canal by the first-born at the time of delivery (12). Through cesarean delivery the first-born is also at a higher risk. The first-born, although usually the twin who is delivered first and attached to the placenta the shortest amount of time, may be exposed to infectious maternal blood longer if the maternal membranes rupture before delivery. It is hypothesized too, that most of the second-born infections occurred at a point in time prior to the delivery, but as stated earlier, is difficult to determine *in utero* (12).

The final time frame in which vertical transmission has been demonstrated to occur is the postpartum period. After birth it has been observed that the HIV virus can be passed via breast feeding. Although this pathway is not thought to be a main channel for transmission, there is evidence that it occurs. In a Van de Perre study of 219 infants born in Kilgali, it was determined that 27-36% of the infants at risk acquired HIV through breast feeding (13). These incidences of postnatal infection appear to coincide with the mother's infection status. For example, cases of postnatal infection from women who themselves were recently infected with the virus suggest that the transmission of HIV may be enhanced during primary infection of the virus (13). Primary infection is characterized by high virus titers and a low antibody titer (3). The same holds true for those women who are in a more advanced stage of the disease. They exhibit high virus titers as well as a low T4 cell count and the rates of transmission are also observed to increase (13).

Regardless of what time frame vertical transmission occurs, determining infant infection is a difficulty in itself. As stated earlier, a newborn's immunity is a result of the IgG antibodies passed to it from its mother. In testing for HIV infection various highly specific serological tests are used. Western Blot assay and enzyme-linked immunosorbent assay (ELISA) are among the most common tests used. These tests test for the presence of antibody to the specific antigen, in this case HIV (3). Polymerase Chain Reaction

(PCR) is another test used to detect HIV. PCR is used to test for either DNA or RNA depending on the type of virus one is investigating (3). A child born to an HIV infected mother may exhibit antibodies, IgG, to the HIV virus without actually having the virus itself. This causes an inaccuracy in testing newborns especially since maternal IgG antibodies may remain in a newborn's system for a period of up to 15 months (14). Therefore testing of newborns for IgG antibodies is unreliable. Recently however, a new assay testing for Immunoglobulin A (IgA), an antibody solely produced by the newborn that is not passed across the placenta from the mother, has been used. This assay has proved 99.7% specific and is overall highly sensitive to the IgA-HIV complex (14). The effects of this have led to earlier diagnosis of HIV infection and thus earlier treatment.

Vertical transmission is the leading cause for the increase in the pediatric HIV infected population. Worldwide this population is growing. What is alarming is the fact that as the number of infected women increase the number of infants infected stands to increase as well. Prevention of pediatric infection can best be obtained through education of the adult populace and prevention of adult infection. Considering transmission rates of 25-30% and the total numbers of infected females of reproductive age, it is estimated that 1800-2000 HIV infected children will be born this year in the United States alone. Of these 2000 children, at least 50% will develop severe disease such as *Pneumocystis carinii* pneumonia within the first year of life (10).

Worldwide vertical transmission threatens to increase the infant mortality rate that had been seeing a hopeful decline. In developed countries such as U.S.A, France, and England, an increase in maternal HIV infection would see a drastic increase in the infant mortality rate of that country. Currently the prevalence of HIV infection among women in most developed countries is less than 1% (15). In Sweden, a developed country, a maternal HIV infection level of 2.4% has been estimated would account for one-third of all infant deaths. A level of 4.8% would account for half of all infant deaths (15). In contrast most developing countries have maternal infection levels of 20+ % (15). In a country such as Uganda, a developing country, a maternal infection level of 30% would

be needed to account for one-third of all infant deaths and over 50% would be needed to account for half of all infant deaths (15). Although the infant mortality rates would be affected more drastically in developed countries, developing countries would still see far greater numbers of children die due to the fact that more children are born in developing countries as opposed to already developed countries (15).

The means by which HIV is transmitted from mother to infant has future implications in various areas of prevention. Increasing our knowledge of mucosal immunity and the role IgA antibodies play can lead to breakthroughs in preventing transmission via the gastrointestinal tract of the infant. The consequence of infection during delivery suggests safer obstetric practices to be observed such as cleansing of the birth canal before and during birth. *In utero* infection while not understood entirely can best be eliminated by prior education and prevention of adult infection. A study performed by Steven M. Wolinsky, a molecular virologist, has shown that there is a possible selection process going on in transmittance of the virus from mother to infant. Wolinsky has found that certain portions of the viral genome are transferred or conserved from mother to infant and are consistent throughout both the maternal and fetal viral genome. As well, other portions are not transferred and therefore do not show up in the fetus' viral genome (16). The implications of this could be astounding. If this selective transmittance is demonstrated to occur with regularity it would be a focal point in developing a vaccine to prevent vertical transmission. A further alternative is for the HIV infected woman not to become pregnant. If, however, that is not an alternative then HIV testing of pregnant women must be done to determine infection status and thus aid in reproductive decisions.

With such a deadly virus running rampant through our population, every possible effort should be made to unravel its deceiving cloak. Although it is of increasing danger to the pediatric population, it affects us all. In the words of Surgeon General Antonia C. Novello M.D. "Let us not speak of victims... Let us not speak of guilt... We have only to speak and think of women, children, men, and families."

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