*Leading Article*

# Current international and national status of paediatric HIV/AIDS

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## The global problem

According to UNAIDS (Joint United Nations Programme on HIV/AIDS) and the World Health Organization (WHO), at the end of 1999, an estimated 1.3 million children worldwide under age 15 were living with HIV/AIDS[1]. The number of children newly infected with HIV in 1999 was estimated to be 620,000. Of these, almost nine-tenths were in sub-Saharan Africa[2]. HIV/AIDS is one of the leading causes of death in children on a global basis and approximately 3.8 million children under 15 have died from the virus or associated causes[3]. The number of AIDS orphans (children who lost their mother or both parents to AIDS when they were under the age of 15), since the beginning of the epidemic, was estimated to be 13.2 million[1].

More than 95 percent of all HIV-infected people now live in developing countries, which have also suffered 95 percent of all deaths from AIDS. In countries with the longest known AIDS epidemics it is reported that children with HIV disease occupy three-quarters of paediatric hospital beds. The HIV epidemic among children is responsible for the slowing, and in some cases the reversal, of the decline in infant and child mortality in the developing world observed during the 1980's. In a cohort study in Kampala, Uganda, the infant mortality was 34 per 1000 live births in infants born to mothers uninfected with HIV, and 336 per 1000 in those infants with laboratory-confirmed HIV infection[4]. In the HIV-infected infants who survived infancy, 34 percent had died by age 1 year, 66 percent by 3 years, and 75 percent by 5 years[4].

## The Sri Lankan scenario

It has been more than a decade since the spread of HIV in Sri Lanka was recognized. With a population of 18 million, it is estimated that about 7300 adults and 200 children (0-14 years) are living with HIV infection as of end December 1999. Estimated deaths in 1999 among the 0-14 year age group due to AIDS was around 100.

HIV/AIDS was first reported in a Sri Lankan in 1987. Up to June 2000, the number of HIV infections reported to the National STD/AIDS Control Programme is 337. There were 5 HIV-infected children amongst this 337, and four deaths. Of these, 4 had acquired the virus from the mother and the other through infected blood transfusions. Age at diagnosis ranged from 1 day to 14 years. One was asymptomatic while the others presented with symptoms and signs of recurrent pneumonia, wasting, anaemia and hepatosplenomegaly.

## HIV transmission in children

Over 90% of HIV infection in children is acquired by transmission from mother to infant. Worldwide, almost two and a half million women are newly infected with HIV each year. Many of these women subsequently transmit the virus to their infants during pregnancy, labour and delivery, or through breast-feeding. It is estimated that mother-to-infant transmission (MTIT) results in 600,000 new infections in infants annually (1600 infections each day)[5]. On a global basis approximately 50% of HIV-infected individuals are women, most of whom are in their child-bearing years.

The rate of HIV transmission from mother to infant varies in different areas of the world. In the absence of any preventive interventions the risk of an infant acquiring the virus from an infected mother ranges from 15%-25% in developed countries and 25%-35% in developing countries. In the United States, large, prospective, placebo-controlled studies have confirmed an expected transmission rate of approximately 25% among HIV-infected women[6,7]. In Europe reported rates of perinatal transmission have been somewhat lower, around 13% to 15%[8,9]. In Africa, where the seroprevalence of HIV is over 20% in many areas, perinatal HIV transmission rates have been reported to be 20-42%[10].

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**Mechanisms of transmission**

Most infected infants acquire HIV infection perinatally or by breastfeeding[10]. Only a minority acquire the infection in utero. Although the precise mechanisms are unknown, it is thought that HIV may be transmitted when maternal blood enters the fetal circulation or by exposure to virus during labour and delivery. The role of the placenta in maternal-fetal transmission is unclear. Many factors influence the risk of perinatal transmission of HIV. These include:

***Obstetric factors***

- Elective caesarian delivery reduces MTIT.
- Premature rupture of membranes associated with higher risk of transmission.
- Instruments at vaginal delivery: use of scalp electrodes, forceps or vacuum extractors and episiotomy increases MTIT.

***Maternal factors***

- Clinically or immunologically advanced HIV disease increases the risk of MTIT.
- Recent infection (seroconversion) increases the risk.
- Vitamin A deficiency increases the risk.
- Chorioamnionitis increases the risk.
- Cigarette smoking increases the risk.

***Fetal factors***

- Preterm infants are at increased risk of infection due to increased susceptibility to intrauterine acquisition of infection and less developed immune systems.
- Low birth weight (<2500g) and /or gestational age of <38 weeks.
- First born twin is at increased risk of acquiring HIV compared to the second-born.

***Viral factors***

- Viral load: High viral load increases the risk of transmission.
- Viral phenotype: Non-syncytium inducing (NSI) phenotype is preferentially transmitted.

**Role of breastfeeding**

Studies have suggested that breastfeeding introduces an additional risk of HIV transmission as high as 28% when women acquire HIV infection during lactation[11] and 14% in the presence of established HIV infection[12-15]. In developing countries it is estimated that one-third to one-half of all HIV infections are transmitted through breastfeeding[16]. The extent to which transmission of HIV in breast milk occurs in early compared to late lactation is not clear. However, transmission from early breast milk is thought to be considerable due to high cellular content of early milk[17]. A study carried out in Malawi in Africa has demonstrated a clear relationship between the duration of breast-feeding and the likelihood of HIV transmission to the infant. The cumulative risk of HIV transmission was 3.5% at 5 months, 7.0% at 11 months, 8.9% at 17 months and 10.3% at 23 months of breastfeeding[18]. However it has been difficult to differentiate between late intrapartum HIV transmission and transmission via breastfeeding.

In countries where safe alternatives to breast milk are readily available and economically feasible, this alternative is being encouraged. Generally, in developing countries where safe alternatives to breast milk are not readily available the benefits of breastfeeding must be weighed against the risks of increased morbidity and mortality associated with failure to breastfeed. However, due to the significant body of evidence demonstrating an increased risk of HIV transmission via breast milk, women should be advised to make an informed choice on whether to breastfeed or not, having considered their individual circumstances.

**Diagnosis**

HIV infection can be definitively diagnosed in most infected infants by 1 month of age and in virtually all infected infants by 6 months, using viral diagnostic assays. The DNA polymerase chain reaction (PCR) assays and HIV culture techniques can identify at birth around one-third of infected infants. With these techniques, approximately 90% of HIV-infected infants are identifiable by 2 months of age, and 95% by 3 months of age. PCR assays evaluate whether there is virus present within peripheral blood mononuclear cells (PMBC). HIV culture is considerably more expensive and less rapid than

PCR. Both methods can provide qualitative and quantitative data. HIV RNA PCR assay which measures free virus in the plasma is more expensive than HIV DNA PCR and is generally not used for early diagnosis.

These viral diagnostic assays are as yet unavailable in Sri Lanka and diagnosis of HIV infection in the very young child may often be difficult. Moreover, all children born to infected mothers have antibodies to HIV due to transplacental transfer of maternal antibodies and this state is maintained up to 18 months of age. Following this period however, only HIV-infected children remain seropositive as confirmed by enzyme immunoassays or western blots. The presence of plasma p24 antigen and a quantitative increase in HIV antibodies in the child compared to the mother are the only methods available for the diagnosis of HIV infection in children under 18 months of age in Sri Lanka. Signs and symptoms suggestive of HIV disease in the child would strengthen the diagnosis.

**Progression of HIV disease in children**

HIV disease progresses more rapidly in children than in adults. The clinical presentation is also very variable. Some children demonstrate a rapid loss of CD4+ cells during the first 2 years of life and progress very rapidly to AIDS-defining conditions. A more intermediate rate of progression is noted in a larger group of children who tend to develop evidence of severe immunosuppression by the age of 7 to 8 years with a much more gradual loss of CD4+ cells. A small group of children continue to remain healthy and have normal to minimally decreased CD4+ cell count even at 8 years of age. Before combination antiretroviral therapy became available for treatment of HIV infection, rapid progressors comprised about 20% of patients, intermediate/slow progressors constituted 60% to 75%, and long term survivors were 5% to 10% of the patient population[19-21]. Data from studies of large numbers of perinatally infected children have shown that the median survival time of perinatally infected children is 8 to 9 years[21-22].

**Clinical presentation and management in paediatric HIV disease**

Most affected infants may show no symptoms at birth. But those who show symptoms of HIV disease in the first 6 months of life are most likely to fall ill and die young. Children in general develop clinical signs of HIV disease earlier than adults.

Many HIV-infected children do not gain weight or grow normally. They are slow to reach important milestones in motor skills and mental development such as crawling, walking and speaking. As the disease progresses many of these children develop neurological problems. Life-threatening opportunistic infections (OI) such as pneumocystis carinii pneumonia (PCP), cerebral toxoplasmosis and cryptococcal meningitis are also seen in HIV-infected children but the incidence of these infections differ among adults and children. Lymphocytic interstitial pneumonitis (LIP), rarely seen in adults, occurs frequently in HIV-infected children. Like PCP, this condition also causes respiratory distress and often leads to hospitalization. HIV-infected children suffer from the usual bacterial infections only more frequently and more severely than uninfected children. These bacterial infections can cause seizures, fever, pneumonia, diarrhoea, dehydration and other complications. Severe, recurrent candidiasis in the mouth and throat lead to difficulties in swallowing.

Routine immunization (except BCG if the infant or child is symptomatic) is recommended for all HIV-infected children. Early diagnosis and prompt treatment of infections, regular growth monitoring, maintaining good nutrition and basic hygiene are essential components of care of HIV-infected children. Treatment with antiretroviral drugs should be considered depending on the availability.

**Antiretroviral treatment in paediatric HIV infection**

A number of very specific scientific and medical concerns need to be considered in the treatment of children with HIV infection even though the basic principles that guide treatment of paediatric HIV infection are the same as for any HIV-infected person. These include age-related issues such as CD4 + cell counts, drug metabolism, special formulations and treatment regimens appropriate for infants and older children. Thus, treatment of HIV-infected children today is a complex task of using potent combinations of antiretroviral drugs to maximally suppress viral replication.

During the early years of the paediatric HIV epidemic, monotherapy with nucleoside reverse transcriptase inhibitor (NRTI) agents zidovudine (ZDV or AZT) or didanosine (ddl) was the standard therapy mainly because there were no other effective agents available. Short-term beneficial effects were observed with monotherapy or with dual combinations[23-26]. However, with the advent of PCR assays it was observed that treatment failure led to increased virus replication and significant increases in plasma viraemia and that a persistently high viral load was a poor prognostic factor in both adults and children. Currently there are 16 drug products approved by the Food and Drug Administration (PDA) in the United States for the treatment HIV infection. Of these, paediatric formulations are commercially available for the following: Zidovudine, Didanosine, Lamivudine, Stavudine, Abacavir, Nevirapine, Ritonavir, Nelfinavir and Amprenavir.

Highly Active Antiretroviral Therapy (HAART) with NRTIs, Non-nucleoside reverse transcriptase inhibitors

(NNRTI) and protease inhibitor drugs modifies viral replication dynamics and slows it significantly[27]. HAART may be well tolerated and is more likely to produce the desired effects of sustained reduction in viral load and an increase in CD4+ counts. There are however, no randomized, controlled trials as yet that clarify which is the best combination for initial therapy or details as to when treatment should be started. Early aggressive treatment of HIV-infected infants may lead to preservation of immune function, but difficulties of long-term tolerability and compliance have to be considered.

**Prevention of mother-to-infant transmission of HIV**

Until 1994, there were only two main strategies for limiting the number of HIV-infected infants; i.e. prevention of women in childbearing age from becoming infected with HIV (primary prevention) and provision of contraceptives and pregnancy termination where this is legal, to enable infected women to avoid pregnancies.

However, the landmark Paediatric AIDS Clinical Trials Group (PACTG) 076 study, a multicentre trial conducted both in the United States and Europe, demonstrated that a three-part regimen of ZDV given during pregnancy, intrapartum and postnatally for 6 weeks to the infant could reduce the risk of mother to infant transmission by 67%[6] in non-breastfeeding mothers. The Bangkok Perinatal Zidovudine Study, a randomized, placebo-controlled trial, showed that a short course of oral ZDV administered late in pregnancy and labour reduced the risk of transmission by 51%[28]. All women were advised not to breastfeed and were provided with infant formula. Other trials with short-course regimens given to pregnant women near or at labour and delivery have also demonstrated reduction in rates of transmission[29-32]. These antiretroviral trials have convincingly demonstrated that prophylactic administration of ZDV to mothers can prevent transmission of HIV in a significant proportion of deliveries. The short-course regimen of the Bangkok perinatal study is recommended for Sri Lanka as it is less costly and more feasible to implement.

**Epilogue**

It is apparent that in the local scene, the diagnosis of HIV infection in children rests mainly on a high index of suspicion in ill children and sero-surveillance of pregnant mothers. Children with unexplained infections, opportunistic infections and apparent immuno-compromisation together with certain high risk factors should be evaluated for HIV infection. Early diagnosis and measures taken for prevention seems to be the only feasible strategy in a country like ours with scarce resources. It is now the time to identify the available resources, develop plans and implement programmes to prevent mother-to-infant transmission of HIV.

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