Editorial

PEDIATRIC AIDS: AN INDIAN PERSPECTIVE

Since its first description in 1981(1), AIDS has in the span of just over a decade assumed the shape of a devastating pandemic–perhaps the worst ever seen by mankind. The disease has been reported from all corners of the globe, but the pandemic is in different stages of evolution in different parts. The projections for the future, especially for the developing countries of South East Asia are grim. The disease has an unprecedented social, economic and behavioral impact on individuals, families, communities and countries and a large number of benefits brought about by modern medicine (like decrease in infant mortality and increase in life expectancy) are likely to be wiped out in years to come. AIDS has reset all our preconceived agendas and time-tables, and as the disease has accelerated its toll around the world, it has spurred an unprecedented worldwide research. Now more is known about the HIV virus, its molecular biology and its targets than any other virus. The modes of transmission are well documented and the epidemiology of the disease, both global and regional, are being understood.

Pediatric AIDS follows adult HIV infection in a population, since the infection in children is invariably acquired from adults. However, since AIDS in children manifests much earlier, children with the disease may be the first indication of infection in a community. During the next decade or so, a bulk of infections in developing countries including India, will be among women and children, most of whom will not belong to any identifiable 'high risk group'.

The Global Scene

Currently, more than 500,000 cases of AIDS worldwide have been reported to the World Health Organization (WHO) from 168 countries, but when under-diagnosis and under-reporting are taken into account, close to 1.7 million adult and 500,000 pediatric cases are estimated to have occurred(2). An estimated 10-12 million adults and 1 million children have been infected with the HIV, and the bulk of these infections have occurred in sub-Saharan Africa. The WHO predicts that by the year 2000 AD the cumulative number of adults and children infected with HIV will rise to 30-40 million and the number of AIDS cases to 12-18 million(3). What is disconcerting is that an estimated 90% of these infections will occur in third world countries–the countries least capable of coping with a problem of this magnitude.

The Regional Scene (South-East Asia and India)

Till the end of 1992 about 1250 cases of AIDS have been reported from this region(3) and 95% of these are from Thailand and India. Estimates, however, put the actual figure close to 20,000. The relatively smaller number of cases is because of the late introduction of the virus in this region, under-recognition and under-reporting.

Data on HIV infection tend to show that though late in starting, the rate of new infections in this region is alarmingly high and reminescent of sub-Saharan Africa of the early 1980s. The following figures from India are revealing: in Manipur, of over 2000

intravenous drug users (IVDU) none were seropositive when tested in 1986-1989 compared to 54% in 1989-90; seropositivity rates among commercial sex workers in Bombay increased from 2% in 1989 to 40% in 1991; HIV-1 seroprevalence among prostitutes in remand homes in Vellore increased from 0.5% in 1986 to 34.5% in 1990(3). Current seroprevalence data from India indicate an HIV-1 positivity of 7.1/1000 population. Extrapolating this data to the whole country it has been estimated that the total number of HIV-1 seropositives is between 0.637-1.0 million(4,5).

It is of significant concern that HIV-2 infection, which was till recently thought to be restricted to the African continent, has been found in significant numbers from different parts of the country(6,7), though the detailed epidemiology of this is not yet known. Projections for the future are indeed gloomy- an estimated 200,000 cases of AIDS and 3.4 million HIV-1 seropositives by 1995(2). The unknown factor of HIV-2 could make the situation even worse. Of all these cases 30-50% cases will be comprised of women and children, an overwhelming majority of who will remain undetected(5). The WHO estimates that while the annual number of HIV-1 infections will peak in Africa by 1995, infections in South-East Asia will continue to increase well into the next century. The annual number of HIV-1 infections by 2000 AD would far exceed that seen in sub-Saharan Africa(3).

In the developed countries of the West, pediatric AIDS constitutes only 2% of all cases, whereas in developing countries, where a greater proportion of women in the reproductive age-group are affected, pediatric AIDS comprises 15-20% of all cases(8). Since there is very little experience and information available in India with regard to pediatric AIDS, we have to of necessity, draw heavily on the lessons learnt in other developing regions, notably Africa, where the socio-economic situations, levels of health and hygiene and access to health care facilities are similar.

Epidemiology

About 80% of pediatric HIV-1 infection is perinatally acquired, and the remaining 20% through parenteral exposure to blood or blood products(9). Infections through breast milk and sexual abuse are other minor routes. As donor screening becomes more widely available and its implementation ensured, an overwhelming majority of the infections seen in India will be perinatally acquired. The perinatal infection is also called vertical, intrauterine, transplacental and congenital, reflecting the uncertainty of its route and timing. The efficiency of transmission by this route is estimated to be between 20-45%, but if the mother is symptomatic, the rates are probably much higher(10). Though there are no clear cut predictors of risk to an infant, there is some evidence to suggest that the rate of transmission is higher in Africa than in developed countries(11). Limited data available suggests that mother to infant transmission of HIV-2 may be less than that of HIV-1(11).

Diagnosis of HIV Infection

For developing countries, the first stumbling block in pediatric HIV medicine is the diagnosis of HIV infections. Since maternal antibodies are passively transferred to the baby, detection of antibodies in the baby *per se* does not indicate infection. Approximately 50% infants loose these antibodies by 10 months, 75% by 12 months and nearly all by 15 months(12). Analogous to passively transferred measles antibodies, there is some evidence to suggest that HIV-1 antibodies from the mother may be lost earlier in

tropical countries(13). Currently, there are no easily available tests to distinguish between the maternal and the baby's antibodies, and since the more sophisticated tests like polymerase chain reaction (PRC) and HIV culture are not likely to be widely available, the policy one would have to adopt is to follow-up babies born to HIV seropositive mothers till they become seronegative or cross the age of 15 months or develop symptoms.

Diagnosis of AIDS

The initial Centres for Disease Control (CDC) definition of AIDS in children less than 13 years of age required documentation of a previous opportunistic infection or AIDS associated malignancy in the absence of a primary or secondary immunodeficiency disorder(14). This definition was revised in 1985 to include lymphocytic interstitial pneumonitis (LIP)(15) and again in 1987 to include a broader range of clinical manifestations(16). This definition is widely used, but is a complex one and relies heavily on laboratory parameters to make definitive diagnosis of opportunistic infections. This fact precludes its use in developing countries. The WHO in 1986, therefore, suggested a simplified set of clinical criteria for the diagnosis of pediatric AIDS in developing countries (*Table I*)(17). Field evaluation of these criteria in African children has shown a sensitivity of between 37%(18,19) and 40%(20) and a positive predictive value between 26%(18) and 59%(19).

The low sensitivity of the WHO criteria is because the clinical signs are poorly defined, do not include pulmonary disease (which is commonly seen in pediatric AIDS), and there is a great deal of overlap with many endemic diseases seen in tropical countries. Also, because of the overemphasis on chronic signs and symptoms, application of the WHO criteria alone will miss out the children who die of acute overwhelming infections. A WHO Working Group that addressed these issues in February 1989, recommended that serologic diagnosis of HIV infection should be made wherever possible and "severe, persistent lower respiratory tract signs" be included as a 'major

TABLE I—*WHO Clinical Criteria for the Diagnosis of AIDS in Developing Countries*(17)

Major signs	Weight loss or abnormally slow growth
	Chronic diarrhea for more than one monh
	Prolonged or intermittent fever for more than one month
Minor signs	Generalized lymph node enlargement
	Oropharyngeal candidiasis
	Recurrent common bacterial infections
	Persistent cough for more than one month
	Generalized dermatitis
	Confirmed HIV infection in the mother

The presence of 2 major signs and 2 minor signs in the absence of other known causes of immunodeficiency is diagnostic of AIDS.

criteria' in the original list. In India, the WHO criteria have been used only in a very limited way, and that too in an older age group of children(21). Since the prevalence of HIV infection is currently low, it is recommended that the WHO criteria be used only after HIV seropositivity has been established or else, an unacceptably high false positive diagnosis will result.

The Clinical Spectrum

AIDS in children differs significantly from the better known illness seen in adults. Children clearly progress faster in developing immunodeficiency and related illnesses. Since most children are perinatally infected, a majority of cases occur in the young and very young. Perinatally infected children have a mean age at diagnosis of 17 months and a median of 9 months, but symptoms may sometimes not manifest till the age of 7 years(22). In children infected by transfusion, the duration between transfusion and diagnosis is longer (mean 24 months, median 17 months).

Children are more likely than adults to have serious bacterial infections, CMV infection, LIP, HIV encephalopathy, chronic parotitis and hypergammaglobinemia. Conditions less common in children are opportunistic infections like toxoplasmosis, cryptococcosis, histoplasmosis and tuberculosis, Kaposi sarcoma, CNS lymphoma and lymphopenia(23). The usual clinical features seen in children cover a wide spectrum of manifestations, but findings such as lymphadenopathy, hepatosplenomegaly, oral candidiasis, failure to thrive, weight loss, chronic diarrhea, prolonged fever, recurrent/serious bacterial infections, LIP and opportunistic infections (tuberculosis, *Pneumocystis carinii* pneumonia) are the commonest features(22). A classification system to elucidate the clinical status of the child has been developed by the CDC (*Table II*)(24).

Symptomatic children fall into class P-2 and are further separated into subclasses and categories by clinical manifestations. Though, this system does not indicate the

TABLE II–*CDC Classification for HIV Infection in Children under 13 Years Age**

P-0	Indeterminate infection in perinatally exposed children less than 15 months with antibodies to HIV	
P-1	Asymptomatic infection	
	A	Normal immune function
	B	Abnormal immune function
	C	Immune function not tested
P-2	Symptomatic infection	
	A	Nonspecific findings
	B	Progressive neurologic disease
	C	Lymphocytic interstitial pneumonitis
	D	Secondary infectious disease
	E	Secondary cancers
	F	Other diseases possibly due to HIV infection (hepatitis, cardiopathy, he matologic disorders, dermatologic disease)

* Abbreviated from MMWR 1987, 36: 225-236.

severity of the disease, it is recommended that all pediatricians become familiar with this, because such a schema greatly facilitates the collection of data on the incidence of various manifestations.

Little is known regarding the HIV-1 presentation in the pediatric population in India. Because of the high mortality from malnutrition and diarrheal and respiratory infections the full impact of HIV infection may not manifest. It has been observed in Africa that a large number of children infected with HIV do not live long enough to develop AIDS as they succumb to common childhood diseases(25). However, certain prominent differences exist in the clinical patterns between children from US/Europe and those from Africa. Babies born to African HIV-1 seropositive mothers have increased rates of neonatal deaths, low birth weight, low gestational age at birth, low head circumference to height and chorioamnionitis, phenomena not seen in the West(11,26).

The progression of disease is significantly faster, and these children do more poorly in the first 2 years of life than their US/European counterparts. For instance, 55 and 44% of infected children had died by 24 months compared to only 20% in the US and France(13,27). A variety of factors like malnutrition, increased exposure to infections, lack of health care facilities and specific therapies may account for the discrepancies but they have not been adequately evaluated. *Pneumocystis carinii* pneumonia (PCP) occurs less frequently in developing countries as compared to the West(28,29) whereas tuberculosis is more common(28,29). Although, initially an interaction between malaria and HIV-1 infection was suspected, it is now known that malaria is no more serious in infected children(31). Kala azar may occur more frequently and with greater severity(32).

Special Issues in Relation to Pediatric AIDS

Breast Feeding: Though it has been documented beyond doubt that HIV-1 can be transmitted through breast milk, the WHO, for valid reasons, continues to support breast feeding by seropositive mothers(33). Transmission through breast milk is very rare, and all available data suggests that breast feeding will protect infants of HIV-1 seropositive mothers from other infections and may prolong survival(34). Since breast feeding is essential for infant survival and growth and the alternatives are neither affordable nor safe, breast feeding by the biological mother should be actively promoted, regardless of the HIV status.

Immunization: The issues under consideration are: (*a*) the risks posed by vaccine preventable diseases (VPD), (*b*) adverse consequences of vaccination, and (*c*) impared efficacy of vaccination.

The consequences of VPD in an unprotected and immunocompromised child will be devastating. Concern is justifiably raised, weather live attenuated bacterial/viral vaccines to immunocompromized children are potentially damaging. In adults, BCG can cause disseminated and fatal disease(35). However, at birth (the age at which BCG is recommended) HIV-1 seropositive children are rarely immunodeficient. BCG given in areas of high HIV-1 endemicity has not resulted in higher rates of adverse effects(36). Although severe disease including paralytic polio has been described in children with congenital immunodeficiency receiving live polio vaccine(37), this has not been reported in HIV-1 seropositive patients. To date, no child with HIV-1 infection has been identified to have encephalitis, neurologic abnormality, pneumonia or death following measles

vaccination(26). Concern has been raised that HIV-1 infected children may not respond optimally to vaccination–but this fear is unfounded. A majority of children respond adequately, though peak antibody concentrations are somewhat lower than in healthy children(38). Besides all these considerations, the age at which vaccinations are recommended, it is not possible to know the HIV status of the child. In view of these, the WHO has recommended the all asymptomatic HIV-1 seropositive children should receive all childhood vaccinations. Symptomatic children should not receive BCG and live polio vaccine(36). This recommendation should be adapted as a National Policy and the existing immunization programme vigorously persued.

Medical Management

Though anti-retroviral therapy is routinely used in the developed countries, the drugs to be used, zidovudine (azidothymidine AZT), dideoxyinosine (ddI), dideoxycytidine (ddC), interferon singly or in combination, the dosing schedule and the optimum time for starting therapy are still being worked out. There is virtually no experience of the use of these agents in children in developing countries. The use of anti-retroviral agents will largely be an academic interest in our country owing to the resource constraints. The mainstay of therapy will be supportive management.

The corner-stones of supportive treatment include maintenance of an adequate nutritional status, routine vaccinations, vigorous treatment of respiratory, gastro-intestinal, skin and mucous membrane infections and the treatment of opportunistic infections amenable to diagnosis and therapy. Tubercular infection, one of the commonest opportunistic infections in developing countries, though difficult to diagnose (cutaneous anergy, atypical *X*-ray findings) is eminently treatable. However, thiacetazone should probably not be used in view of the reactions seen with this drug in patients with AIDS(39). Treatment protocols for PCP, oral/esophageal candidiasis, *Toxoplasma gondi, Herpes simplex* and *Varicella zoster,* and cryptococcal meningitis are available, but the ideal management of cryptosporidium, CMV and *Mycobacterium avium/intracellulare* is uncertain(9). Prophylactic treatment with co-trimoxazole for PCP for all children less than 1 year and for all symptomatic children(40) (alternatively, if CD4+ counts are less than 400/mm^3 in order children) is advisable. Isoniazid prophylaxis to a similar group of children is also probably required(39), though the problems of resistance, hypersensitivity and compliance with such treatment have not been worked out(41).

A large number of children with AIDS can be expected in the years to come, and given the resource constraints of health care systems, there is an urgent need to start examining ways in which health care can be delivered to a large number of children with AIDS without infringing on the other primary care activities. The existing Western treatment models with the use of anti-retroviral agents are not relevant to our country and there is an urgent need to develop low cost supportive treatment protocols given our local conditions and health infrastructure. The WHO has developed protocols for the clinical management of AIDS for adults and children in the form of flowcharts (clinical algorithms)(42). These address three levels of health care facilities: health centres, district and referral hospitals. These protocols have till now not been widely tried. It is imperative that based on these guidelines an adaptation be made for Indian conditions for clinical care, planning of care services, costing of resources and clinical training.

The prognosis of pediatric AIDS is uniformly poor, and roughly 3 patterns have emerged. In perinatally infected children, those that are diagnosed before the age of 1 year have a median survival time of 9-12 months and usually die of PCP. Children diagnosed after the age of 1 year have a median survival period of 31.5 months if PCP does not occur(43). Older children infected by blood/blood product transfusion have a median survival of 12-16 months after the diagnosis of AIDS(44). In India, what proportion of children will progress to symptoms, oppotunistic infections, malignancy or death cannot be predicted with any degree of certainty, but is likely to be worse than in the West. In our own modest experience of 9 children with transfusion related AIDS, managed on supportive treatment alone, 3 children diagnosed 18 months back and 3 out of 6 children diagnosed 24 months back are alive.

Social, Economic and Other Related Issues

Poverty is a key factor that contributes most heavily to the spread of AIDS according to the WHO's first full scale progress report on the Global Programme on AIDS(45). Financial hardships lead men to leave families to find work; promotes drug use and makes prostitution a survival strategy for women. AIDS then completes the full cycle by making the community even poorer. The full brunt of the socio-economic ramifications of this epidemic is being felt in Africa, and will soon be seen in India. In some African countries, infant mortality rates have risen sharply, and much of the benefits of Child Survival Programmes made over the last 10 to 15 years, wiped out(46). In some areas, 80% of hospital beds are occupied by patients of AIDS related illnesses(47). Millions of children have lost one or both parents through AIDS, thus creating a new problem of "AIDS orphans". These orphans face severe deprivation and add to the childhood morbidity and mortality.

Pediatric AIDS then represents a condition that is relevant to a wide range of medical specialists including neonatologists, pediatricians, perinatologists, obstetricians, infectious disease specialists and oncologists. Because the diagnosis, management and prevention of HIV infection includes a focus on mothers, infants and families, frequently in a setting of severe social disruption and poverty, the involvement of social workers, psychologists, counsellors as well as health administrators, sociologists and community workers along with local, state and central policy makers, will be essential. Either directly or indirectly pediatric AIDS is bound to touch all our lives, both as pediatricians and as human beings.

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