

# Review Article

## HIV Infection in Infants and Children - An Updated Review

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The first cases of Acquired Immunodeficiency Syndrome (AIDS) were reported in United States in 1981. AIDS appeared in Bangladesh 8 years later. At present AIDS exists worldwide. Neighboring countries like India, Myanmar and Thailand already have alarming rates of HIV infection. With increasing incidence and prevalence of AIDS worldwide, Human Immunodeficiency Virus (HIV) infection in infants and children are also increasing. In developed countries, paediatric AIDS constitute only 2% of HIV infection, where as in developing countries, it comprises about 20% of all the HIV infected cases. Areas like Africa, where HIV is endemic and heterosexual transmission predominates, have a devastating high frequency of paediatric AIDS cases<sup>1</sup>.

In contrast to adults the course of HIV infection in children is accelerated, the phases are less distinct and progression from one phase to another is rapid resulting in early death<sup>2</sup>.

### How do children have HIV?

Nearly all new cases of HIV infection in children are acquired during gestation, at birth or via breast milk. The term vertical transmission from mother to child is used to encompass prenatal, perinatal and postnatal transmission of infection from mother to child. Maternal antenatal viral load and antiviral therapy are associated with both in utero and ante-partum transmission. Low birth weight is significantly associated with in-utero transmission while antenatal CD4 cell percentage, birth weight and duration of membrane rupture are associated with intrapartum transmission<sup>3</sup>. There is also risk of infection via blood transfusion, e.g., in patients with thalassemia major or chronic blood transfusion<sup>4</sup>.

### Pathogenesis of HIV

HIV is known to consist of a heterogenous group of viruses transmitted to hosts either by infectious particles or by virus infected cells. The mucosal lining

of bowel or uterine cavity could be the initial site of infection. Alternatively, lymphocytes and macrophages in these tissues or cervix and urethra could be infected by cell transmission of the virus.

Acute virus infection is followed by spread primarily to lymphoid tissue and peripheral blood cells. Virus attaches to cellular receptor followed by fusion and nucleocapsid entry into cells.

Virus replication in cells is influenced by intracellular factors and controlled by cellular immunity (CD8 T cell response). With gradual loss of CD4 cell function and number and also loss of CD8 antiviral activity, there is release of infectious virus and ultimately increased number of virus infected cells. Enhanced viral replication leads to emergence of pathogenic strains. There is further loss of CD4 cells and function and development of AIDS ultimately<sup>5</sup>.

### Systemic effects of HIV in children

#### *Central nervous system*

Vertically transmitted HIV infection occurs in immature and developing stage of brain. The major cell type infected in brain is monocyte-macrophage. After the infection peripheral monocytes transport the virus across blood brain barrier into the central nervous system (CNS). HIV replication in these infected cells leads to release of cytokines or proteolytic enzymes that are toxic to neural cells, thereby inducing further infiltration of inflammatory cells. Demyelination and neurological cell death is a direct result of HIV infection<sup>6</sup>.

In children HIV may have a direct or indirect impact on the developing brain, may lead to global or highly specific consequences and may be responsible for minor cognitive consequences or conversely long term and severe disability<sup>7</sup>.

#### *Lymphoid organs*

The presence of lymphadenopathy, hepatomegaly or splenomegaly is taken as strong evidence of HIV in infants born to women infected by HIV in developed countries. Generalized lymphadenopathy is one of the minor signs for diagnosis of AIDS in modified Bangladeshi criteria of AIDS in children<sup>8</sup>.

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However, it has been found to be a relatively common presentation in children with HIV infection in India<sup>9</sup>.

#### *Respiratory system*

Lung is the most commonly involved organ in AIDS. Tuberculosis and opportunistic infections (e.g., pneumocystis carinii, atypical mycobacterium) are common in AIDS. Non-infectious conditions of lungs in AIDS include Kaposi's sarcoma, lymphoid interstitial pneumonitis and alveolar proteinosis<sup>10</sup>.

Lymphoid interstitial pneumonitis (LIP) affects 30-50% of vertically infected children. LIP is a slowly progressive lung disease characterized by infiltration with small lymphocyte and plasma cells. The child often has no symptoms and signs initially despite marked abnormalities like bilateral reticulonodular infiltrates on chest radiograph. Cough, shortness of breath, hypoxia and digital clubbing may develop with time. LIP may coexist with other infections<sup>11</sup>.

Without prophylaxis half of all the children with AIDS will develop pneumocystis carinii pneumonia (PCP), at some time during their illness. PCP leads to respiratory failure and is associated with high mortality. Children with severe immunodeficiency are at particular risk of non-tubercular mycobacterial infection<sup>4,12</sup>.

#### *Gastrointestinal system*

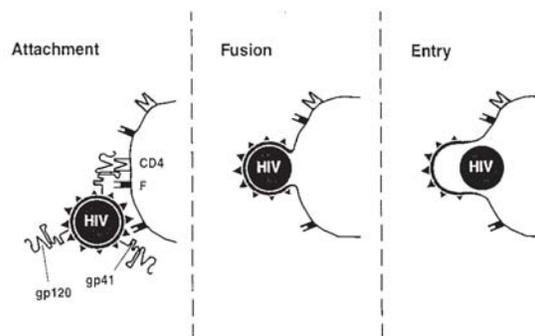
In children with AIDS, gastrointestinal infections with candida, herpes, cytomegalovirus and other intestinal pathogens are more severe, often relapse and are harder to eradicate. Gastritis, enteritis, colitis and proctitis may occur<sup>13</sup>. Intestinal dysfunction with malabsorption of fat, carbohydrate and protein is a common feature<sup>14,15</sup>. Cytomegalovirus, the most virulent organism, can cause necrosis, perforation and often death<sup>16</sup>.

Lymphoma, smooth muscle tumor and Kaposi's sarcoma are the most common neoplasm encountered in children with AIDS<sup>17</sup>.

#### *Hepatobiliary system*

There are reports of AIDS related cholangitis in children. Clinical features are fever, abdominal pain, biliary obstruction and hepatomegaly<sup>18</sup>.

Pancreatitis is common in pediatric population with AIDS and is associated with exposure to certain drugs like trimethoprim- sulphamethoxazol, especially when absolute CD4 T lymphocyte count is less than 100 cells/cumm<sup>19</sup>.



**Fig-1:** HIV cell entry: 3 main steps involved in virus infection of cells



**Fig-2:** Viral and immunologic events in persistent stage (long term) survivors. HIV infection of CD4 cells is placed into a relatively latent state by cells of CD8 T cells and their antiviral factor-a response increased through TH cell cytokines

#### *The heart*

Dysrhythmia, haemodynamic abnormalities, congestive heart failure, unexpected cardiac arrest and death with cardiac dysfunction are common in HIV infected children. Correlates of cardiac function abnormalities include encephalopathy (autoimmune nervous system dysfunction), Ebslein-Barr virus (EBV) co-infection, autoimmune-imbalance and neuropathy, focal lymphocyte infiltrates in heart analogous to LIP in lung in paediatric HIV disease<sup>20</sup>.

Cardiometabolic problems in children with HIV have recently began to emerge like high rates of unfavourable lipid profile, insulin resistance, cardiovascular inflammation and vascular stiffness as well as truncal obesity and facial and extremity wasting. They require monitoring and often intervention<sup>21</sup>.

#### *Renal disease*

Focal glomerulosclerosis and mesangial hyperplasia, are the most common type of nephropathy. The

nephrotic syndrome also occurs and may be the presenting sign in patient as early as 5-6 years<sup>22</sup>.

#### *Skin disease*

The appearance of oral candidiasis in an HIV seropositive child suggest that critical function in cell mediated immunity has been lost and AIDS onset may be near<sup>4,23</sup>.

#### **Clinical features and diagnosis**

Babies with HIV infection appear normal at birth. Definitive diagnosis can be made if the infant develop clinical features of AIDS. A wide variety of symptoms and signs occur among infants and children. Poor growth, failure to thrive, interstitial pneumonia and hepatomegaly occur in nearly all cases of paediatric AIDS. Systemic and pulmonary findings predominate in western countries whereas chronic diarrhoea, inanition and wasting are more common in Africa, where the entity is known as slim disease. Serious recurrent bacterial sepsis and relentlessly progressive neurological disturbances are characteristics of paediatric AIDS and are unusual in adults<sup>11</sup>.

The World Health Organisation has clinical case definition of AIDS in children<sup>24</sup>.

Major signs: Weight loss or failure to thrive

- Chronic diarrhoea more than 1 month
- Prolonged fever more than 1 month

Minor signs: Generalized lymphadenopathy

- Oropharyngeal candidiasis
- Repeated common infections (otitis, pharyngitis)
- Persistent cough more than 1 month
- Generalized dermatitis
- Confirmed maternal HIV infection

Paediatric AIDS is suspected in an infant or a child presenting with at least two major signs associated with at least two minor signs in absence of known causes of immuno-suppression.

With HIV infected children in India, the most common presenting symptom is fever followed by chronic diarrhea, cough, generalized lymphadenopathy, hepatosplenomegaly and skin manifestations. Among bacterial infections pneumonia, otitis media, parotitis and tuberculosis are most common<sup>25</sup>. Majority of children present with poor nutritional status and immunosuppression along with clinical manifestations<sup>26</sup>.

Opportunistic infections continue to be the presenting symptoms of HIV infection among children whose HIV

exposure status is not known (e.g., because lack of maternal antenatal HIV testing)<sup>27</sup>.

Passively acquired maternal antibodies persists until 18 months of age. In the absence of HIV related signs serosal HIV-1 antibody persists until 18 months and persistence of HIV antibody after 18 months is the standard mode of diagnosis. Recent technological advances such as polymerase chain reaction, viral culture and P24 antigen testing have improved early diagnosis in developed countries. However, they may give false negative results in the first 3 months. Other indicators of infection include low CD4 count for age with reversal of CD4/CD8 ratio and high immunoglobulin level. Ideally a second virological test of a separate specimen should be done to confirm an initially positive test result<sup>4,11</sup>.

#### **Natural history of HIV infection**

Children with untreated natural infection progress rapidly to disease especially in resource poor settings where mortality is greater than 50% by 2 years of age. Antiretroviral therapy has the potential to rewrite the natural history of HIV but is accessible only to a small number of children needing the therapy<sup>28</sup>.

#### **Management**

All HIV exposed children should be evaluated by a physician. All HIV exposed babies should receive clotrimoxazole<sup>24,29</sup>. Clotrimoxazole (CTX) prophylaxis is universally indicated starting at 4-6 weeks after birth and maintained till ceassation of risk of HIV transmission and exclusion of HIV infection. Clotrimoxazole protects from infections with high mortality which are more common or more likely to occur in HIV exposed infants and immuno-compromised children. The aim is to reduce the morbidity and mortality associated with malaria, bacterial diarrhoeal diseases and pneumonia in addition to prevention of PCP (pneumocystis pneumonia) and toxoplasmosis<sup>24,29</sup>.

HIV exposed children less than 18 months of age are monitored for signs and symptoms suggestive of HIV disease and opportunistic infections. Antibody testing are offered from 9-12 months of age. When HIV infection is confirmed, HIV is staged by CD4 assessment, if not possible by TLC (total leucocyte count) or clinically. Antiretroviral therapy (ART) is started in advanced stages. Others who are not on ART are monitored by clinical evaluation and CD4 counts every 3-6 months, more frequently in infants and younger children. However, ART can be started

after presumptive diagnosis of severe immunodeficiency even if there is no confirmed HIV diagnosis<sup>24</sup>.

Recommended first line ART regimen includes 2 nucleoside reverse transcriptase inhibitors (NRTI's) and 1 non nucleoside reverse transcriptase inhibitor (NNRTI). ARTI includes lamivudine plus any one of the zidovudine, abacavir or stavudine. NNRTI is nevirapine or efaviranz<sup>24,29</sup>.

A team effort by health care worker, the caregiver and the child is required to ensure long term adherence and good response to ART. ART drug toxicity include diarrhoea, nausea, vomiting, pancreatitis, allergic reaction, myopathy, behaviour changes, etc. In severe and life threatening reactions all ARV drugs are discontinued, another drug is substitute for the offending drug and supportive treatment is given. But ART is continued in mild and moderate reactions along with symptomatic treatment<sup>24,29</sup>.

Immune reconstitution inflammatory response, the apparent clinical worsening due to paradoxical immune response by reconstituted immune system after initiation of antiretroviral therapy may occur in some children<sup>27</sup>.

Common opportunistic infections in HIV infected children are mycobacterium avium complex, pneumocystic jerovii pneumonia, candidiasis, penicillosis cryptococcosis, herpes simplex virus, herpes zoster virus, cytomegalovirus infection, cryptosporidiosis. Diagnosis should be established by clinical manifestation and laboratory investigations. Appropriate treatment should be given<sup>24,29</sup>.

#### **Immunization of HIV positive children**

Children with clinical or laboratory evidence of HIV infection can have diphtheria, tetanus, pertussis, inactivated poliovaccine, but not measles vaccine. Hyperimmune immunoglobulin can be offered following significant exposure. BCG vaccination is not currently recommended for them in UK. The hepatitis B status of all mothers should be checked and infant immunized if appropriate. The WHO is of the opinion that where mortality from natural infection is higher, immunization to the live vaccine outweigh the theoretical risk<sup>24,27</sup>.

#### **AIDS vaccine**

Search for AIDs vaccine began with great optimism and expectations. With the identification of HIV as the cause of AIDS, it seemed that a vaccine will follow

closely behind. But despite a large concerted effort the problem has proven more difficult than anticipated and progress has not matched the initial hopes<sup>30</sup>.

#### **Conclusion**

According to World Health Organisation, nearly 1150 new children are getting infected with HIV everyday. More than 90% of them are in the developing countries, most being the result of transmission from mother to child. The prompt initiation of treatment and a careful selection of first line regimen with adequate potency and tolerability remains central to the management. In addition occurrence and prevention of opportunistic infections, adherence to treatment as well as long term psychosocial consequences are becoming more and more relevant.

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