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Vertical Transmission of HIV: A Review on Epidemiology, Pathogenesis, Prevention, Treatment Strategies and Toxicity of Drugs

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Abstract: Acquired Immunodeficiency Syndrome (AIDS) is the most fatal disorder caused by Human Immunodeficiency Virus (HIV) infection. There has not been any successful chemotherapy developed so far and the infection continues to plague many countries across the globe through last two and a half decades. Heterosexual contact is the predominant mode of transmission among women of childbearing age and consequently the infants are afflicted. Vertical transmission is one of the major etiological factors for HIV/AIDS in children. The infection is symptomatic in the beginning and subsequently progress rapidly. Co-morbidity and rate of mortality is high. Notwithstanding, tremendous progression of technical and scientific capabilities, the world is still not able to control the epidemic of vertical transmission. As of December 2006, about 2.3 million children are living with HIV and the death figures reach 0.38 million. In view of the deteriorating situation of the mortality and co-morbidity of HIV infection among children and lack of literature on vertical transmission, an attempt was made to review some of the crucial publications. Our study correlated some of the important aspects on epidemiology, pathogenesis, co-morbidity, mortality, prevention, treatment strategies (both HIV infection and co-morbidity) and toxicity of drugs. It is concluded that further deterioration in the present status of HIV infection could be avoided by giving priority to developing effective strategies and preventive measures to target the properties of transmitted viruses.

Key words: Vertical transmission, pathogenesis, prevention, treatment, drugs, toxicity

INTRODUCTION

In children, HIV/AIDS was first recognized in the year 1982 and at the end of 1987, 251 cases were reported in Europe (Mok, 1988). The infection continues to plague many countries across the globe through 25 years. It is prevalent allover the world, but more rampantly in Africa, United States, China and India. Heterosexual contact is the predominant mode of transmission of HIV among adults, including an increasing number of women of childbearing age. In addition to different known routes of HIV transfer, recently, it is documented that infected cells and free viral particles present in semen of an HIV-positive person are carried to the woman and ultimately to the offspring (Shehu-Xhilaga *et al*., 2005). The vertical transmission can occur: Before birth by microtransfusion of maternal blood across the placenta, during labor and delivery by exposure to maternal cervicovaginal secretions and blood and after birth through breastfeeding (Cibulka, 2006). Breast-milk transmission continues to account for a large proportion of cases of HIV-1 worldwide (McFarland *et al*., 2006).

The clinical spectrum of HIV in children is vast and ranges from asymptomatic infection to the last stage disease, which manifests as AIDS. The first presentation of HIV infection in children includes signs and symptoms that are not specific-fever, diarrhea, respiratory infections, generalized lymphadenopathy and hepatosplenomegaly (Mok *et al*., 1987). As the disease advance, numerous maternal parameters, including advanced clinical stages, low CD4+ lymphocyte counts, high viral load, immune response and disease progression have been implicated (Ahmad, 2005). Along the progression of HIV/AIDS, several patients are affected by several

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diseases in different systems of the body, in addition to opportunistic infections. The affliction may be either due to disease or as an adverse effect of the drugs used to cure the disease and/or the co-morbidity (Mok, 1988).

As of December 2006, about 2.3 million children are living with HIV. The estimated deaths of HIV-infected children are 0.38 million (AIDS epidemic update). In view of deteriorating situation and lack of literature, an attempt was made to review some of the crucial publications. Our study correlated the important aspects of epidemiology, pathogenesis, co-morbidity, mortality, prevention, treatment strategies (both HIV infection and co-morbidity) and toxicity of drugs.

EPIDEMIOLOGY

The HIV/AIDS epidemic is increasingly becoming a predominant cause of childhood morbidity and mortality in the world. The figures estimated in the developing countries in the early years of 2000 were a total of 800,000 children infected with HIV and 580,000 children die of AIDS-related illnesses every year (Takeb *et al*., 2004). WHO estimates in mid 90s, showed that 1000 new pediatric HIV infections would occur every day with 67% in Africa and 30% in South and Southeast Asia (Dollfus, 1997). Hosnain (2005) observed 700,000 children to be living with HIV around the world in the year 2003, when the world population had a total of 3 million people living with AIDS. Estimates by the WHO and the joint United Nations program on HIV/AIDS showed that HIV prevalence among pregnant women of over 1% have been documented in Djibuti, Sudan and some areas of Somalia (Obermeyer, 2006). In Saudi Arabia, HIV cases have been reported from all regions, but the highest prevalence was observed in Jeddah and Makkah in the western province. The epidemiological data reported from Saudi Arabia during 1984 to 2001 showed a total of 6046 cases diagnosed in both the local and expatriate population. Among this 340 were infected Saudi females and 1376 non-Saudi females (Madani *et al*., 2004).

With a rapid increase in the epidemic of HIV/AIDS in the recent years, China is facing a major crisis especially in the western areas. This is reported to be emerged mainly by mother-to-child transmissions (Hu *et al*., 2006). A survey of the rural areas of central-eastern China revealed 5.9% of the 169 children were HIV positive. Subsequently, in the year 2001, a survey of 224 children showed 4.9% were positive. Of children born to HIV positive mothers, 28.9% were infected (Wang *et al*., 2005). Zhao *et al*. (2006) reported 650 children were living with HIV infection in the 6 provinces of China. Among this 405 were male children and 245 were female children. Transmission routes included mother-to-child transmission (75.1%), blood transfusion/plasma donation (15.7%) and Injecting Drug Use (IDU, 0.5%). In Phillipines, most of the transmission to children is not vertical, but is direct. There is high incidence of child sexual abuse and child prostitution which had left a significant number of children infected with HIV (Tantoco, 1993).

In India, the estimated overall 4.58 million people were living with HIV/AIDS (Muniyandi *et al*., 2006). In a study on clinical manifestations of 92 antiretroviral-naïve children admitted in Pediatric HIV Clinic in Mumbai during the years 1999-2003, Shah (2006) showed that CD4% was higher in infants and lower in children over 5 years of age. Boys had a higher absolute CD4 count than girls. In another study (1996-2000) on 58 HIV-infected children in South Indian Center for AIDS Research and Education, thirty-nine (67.2%) were male with mean age 4 years. Perinatal transmission was the predominant mode of HIV acquisition (67%) (Madhivanan *et al*., 2003).

A survey of pediatric AIDS incidence in Europe and the USA between 1985-1996 revealed that among the European countries with > 100 cases, the steepest rises were seen in the UK. However, in 1985-1987, rates were substantially higher in USA than in any European country. During 2005, an estimated 92% of AIDS cases reported among children in the United States were attributed to mother-to-child transmission of HIV (MMWR, 2006). In Spain, the incidence was from 4.4-16.5 in every million cases. Very elevated rates were observed in Romania, with an incidence of 120.4 per million in the early 1990s. In some countries (Germany, Greece, Denmark, Austria and the Netherlands) AIDS incidence rates were < 2 cases per million children in 1994-1996. The estimated number of children born each year to an HIV-positive mother ranged from 313-546 in northern Italian regions (Girardi *et al*., 2002). In Germany, the average prevalence of HIV seropositivity from 1993-1997 among women bearing children was 0.57 per 1000 in Berlin and 0.14 per 1000 in Lower Saxony (Hamouda, 2003). Gray (1997) showed that the prevalence of HIV infection in pregnant women outside Southeast England has remained relatively constant at around 0.01%, since monitoring began in 1990. By contrast, HIV seroprevalence in pregnant women in London and Southeast England has increased steadily, reaching 0.26% in inner London in 1995. In Brazil, a study (1996-2001) on 76 pregnant women infected with HIV and paired with their 79 exposed infants revealed that 88% of the pregnant women were infected due to sexual practices. Elective cesareans were performed in 57%. The mean gestational age at delivery was 38 weeks and it was revealed that 12.5% were cases of

pronatis; 97% had a ruptured membrane time after less than 4 h and one child (1.3%) was nursed.

Studies on perinatal exposure to HIV in Australia, during 1982-1994 showed that there were 91 women diagnosed with HIV infection who had had 111 perinatally exposed children. While the rate of perinatal exposure to HIV was highest in the Australian Capital Territory and New South Wales, the rate was substantially lower than the rate of diagnoses of HIV and AIDS in women of child-bearing age. Overall, exposure to HIV was attributed to heterosexual contact only, injecting drug use or receipt of blood or tissue by 48, 31 and 18% of women, respectively. The HIV transmission rate to children born to women diagnosed with HIV infection before delivery was 21.6% (McDonald *et al*., 1997).

The WHO (UNAIDS) estimate (AIDS epidemic update, 2006) for the incidence of children afflicted with HIV and AIDS as of December 2006 is as follows:

- Children living with HIV are 2.3 million out of a total HIV cases of 39.5 million on an average.
- Children, newly infected with HIV are 0.53 million out of a total of 4.3 million cases on an average.
- Deaths in children afflicted with AIDS are found to be 0.38 million out of a total number of 2.9 million cases on an average.

According to WHO (UNAIDS) estimate (AIDS epidemic update, 2006) the incidence of children living with HIV, newly infected and deaths in different geographical areas of the World is as follows:

- The order of incidence of children living with HIV/AIDS is Sub-Saharan Africa > South and South East Asia > Latin America > Middle East and North Africa > Caribbean > North America > Eastern Europe and Central Asia > East Asia > Western and Central Europe > Oceania.
- Children newly infected with HIV/AIDS were in the order of Sub-Saharan Africa > South and South East Asia > Middle East and North Africa > Latin America > Eastern Europe and Central Asia > East Asia > Carribbean > Oceania > North America > Western and Central Europe.
- Children who died with HIV/AIDS were of the order of Sub-Saharan Africa > South and South East Asia > Middle East and North Africa > Latin America > Eastern Europe and Central Asia > Carribbean > East Asia > Oceania > Western and Central Europe (AIDS epidemic update, 2006). The HIV/AIDS is found to be in a worst condition in Sub-Saharan Africa and South and South East Asia regions of the world. The incidence of newly infected children is low in western and central Europe and North America. These zones also have the lowest rate of deaths due to the infection.

PATHOGENESIS

In recent studies conducted in SIV-macaque model and in HIV-positive patients, the progression of infection is adequately highlighted. During the acute infection period there is massive and irreversible depletion of CD4 memory T cells. Hence, lymphoid tissue plays a central role in the early stages of HIV pathogenesis (Centlivre *et al*., 2007) . The susceptible CD4 T lymphocytes become infected with HIV and develop infection leading one and half days later to a release of a large number of new virions and the death of the host cell. These virions are cleared from plasma and initiate a new round of infection in susceptible CD4 cells, more in the lymphoid tissue (Veugelers and Schechter, 1997). The chronic stage of HIV infection has been extensively described as a slowly evolving phase, in which the virus induces T-cell death slightly faster than the human body is able to recover (Centlivre *et al*., 2007). Billions of new HIV virions may be produced in an infected individual daily and up to two billion CD4 cells may be killed and replaced daily. The depletion of CD4 and immunodeficiency start to surface, when the body's ability to replace CD4 cells is exhausted (Pontesilli *et al*., 1997).

Majority of HIV-infected neonates and infants have a higher level of viremia and develop AIDS more rapidly than infected adults. Sundaravaradan *et al*. (2006) found that the increased replication of HIV in cord blood compared with adult blood mononuclear cells is regulated at the level of HIV gene expression, resulting in a higher level of viremia and faster disease progression in neonates than adults. In a study on 80 children born to HIV-positive mothers (ANRS 049 Ditrame project, Abidjan, Cote d'Ivoire), Rouet *et al*. (2003) observed that positive viral load was significantly lower among children who were infected in utero than in children who were infected later. Furthermore, disease progression or death was found to be more rapid in girls than boys. Dollfus (1997) reported that perinatally infected children show two types of progression, a precocious form that is usually fatal by the 4th year and a less rapidly progressing form in which survival exceeds 80% at age 7. HCV infection and rapid disease progression is often found in children coinfected with thalassemia major (Shivraj *et al*., 2006).

CO-MORBIDITY

General infections and diseases: At different stages of HIV disease (asymptomatic form, persistent generalized lymphoadenopathy, pre-AIDS and AIDS), children are subjected more to bacterial infections, which are more recurrent, prolonged and painful than those in immuno-competent children (Dollfus, 1997). Nurtaev *et al.* (2005) reported that HIV-positive children are more often infected by virtually all parasites, such as Giardia lamblia, Cryptosporidium parvum, Chilomastix mesnilli, Entamoeba coli, Iodamoeba butschilli, Entamoeba histolytica/dispar, Endolimax nana, Blastocystis hominis, Enterobius vermicularis, Ascaris lumbricoides and Hymenolepsis nana. Opportunistic infections like tuberculosis and pneumocystis carinii are frequently observed in the HIV-infected children (Kaul and Patel, 2001).

In a study on the population of Tashkent, the highest infestation was found to be with intestinal protozoa, including nonpathogenic amoebas and helminths. The patients were found to have gastrointestinal diseases, allergic dermatoses and skin depigmentation foci (Nurtaev *et al*., 2005). HIV surveillance and screening programs established at Khartoum Teaching Hospital, Sudan (during the period 1985-1995) found 15 children with symptomatic HIV infection. Among these patients, pulmonary disease was described as the major cause of morbidity and mortality in pediatric AIDS, manifesting itself in more than 80% of cases. The most common causes of morbidity and mortality were Pneumocystis carinii pneumonia, lymphocytic interstitial pneumonitis, recurrent bacterial infections, which include bacterial pneumonia and tuberculosis (Khare and Sharland, 1999). The co-morbidity common to Saudi patients was generalized lymphadenopathy, oral or vaginal thrush, oral hairy leukoplakia, recurrent herpes simplex, herpes zoster, moluscum contagiosum, condyloma acuminate, thrombocytopenia or aphthus ulcers (Madani *et al*., 2004).

In Brazil, a study of 76 HIV-infected pregnant women, revealed 14.5% of the cases were co-infected with Hepatitis C, 9.2% with Syphilis; 67% were found to be on HIV clinical symptomatology and 9.2% had opportunistic infections (Fabbro *et al*., 2005). The oral examinations performed at Pediatric AIDS Outpatient Clinic, Brazil and School of Dental Medicine, New York, USA, revealed a high frequency of viral infection was detected in the oral cavity (Grando *et al*., 2005). Ziegler and Palasanthiran (1997) showed that 15-20% of the pediatric HIV positive children in Australia, developed severe immune deficiency, opportunistic infections and, in most cases, encephalopathy.

Twenty one HIV-infected children were diagnosed as having cryptococcosis in a Childrens' hospital in Thailand during 1994 and 2001 (Likasitwattanakul *et al*., 2004). The study concluded cryptococcal meningitis as the most common clinical presentation of cryptococcosis. In a study on 58 HIV-infected children (Center for AIDS Research in South India), Madhivanan *et al.* (2003) observed clinical presentations of oral candidiasis (43%), pulmonary tuberculosis (35%), recurrent respiratory infections (26%), bacterial skin infection (21%), paulopruritic dermatitis (19%), hepatosplenomegaly and lymphadenopathy (14%) and chronic diarrhea (7%) among the South Indian children. Studies on 92 antiretroviral-naïve children showed some cases with lymphadenopathy had a high CD4 count, whereas patients with HIV cardiomyopathy had low CD4 counts among Bombay children (Shah, 2006). Diagnosis of two hundred and fifty children in Children's hospital Aligarh, India for tuberculosis revealed 5 cases of HIV positive giving a seroprevalence of 2% (Shahab *et al*., 2004).

Cutaneous and skin infections: Cutaneous and skin infections tend to occur early in the course of HIV infection in children. With progressive deterioration of the immune system, cutaneous infections become more specific and include organisms or disease patterns typically not seen in immunocompetent children (Rennert, 2005).

Bacterial sepsis, is another health problem related with skin, which is described as major cause of morbidity in infants born to HIV-infected mothers in Haiti (Noel *et al*., 2006).

Neurological manifestations: Children suffering from HIV infection suffer from a wide range of neurological deficits, which are frequently apparent by 3-6 months in the severe form. The most pronounced are the motor and cognitive deficits observed in many patients in the latter stages of infection. The postmortem inspection shows cortical atrophy and widespread neuronal loss. One of the most debilitating of the HIV-related syndromes is AIDS-related dementia (Wallace, 2006). The author reported that with the introduction of active antiretroviral drugs, incidences of encephalo- and myelopathy and polyneuropathy were found to increase among the HIV positive cases. Infants with HIV encephalopathy may suffer painful sensations from mild stimuli and extreme irritability and spasticitiy (Dollfus, 1997).

Cardiovascular complications: The antiretroviral treatment-induces lipid abnormalities, which cause an

increase in the incidence of vascular complications in the children (Monforte and Bongiovanni, 2005). In women, the advancing HIV infection is associated with venous thrombotic events (Levine *et al*., 2006).

Hepatic manifestation: The HIV infection is reported to be often acquired in cases already infected with hepatitis B and C viruses (Guan, 2005; Caballero *et al*., 2005). Both HIV and Hepatitis C Virus (HCV) can be transmitted from mother to child during pregnancy and delivery. Vertical transmission of HIV and HCV separately is most likely from HIV/HCV co-infected mothers (Caballero *et al*., 2005). Coinfection with hepatitis C virus and HIV is a known risk, which cause liver fibrosis associated with hepatotoxicity (Aranzabal *et al*., 2005).

Renal complications: The HIV positive patients develop renal insufficiency. The renal biopsy of some patients showed lesions of thrombotic microangiopathy and malignant hypertension with development of the stages of vascular and glomerular damage (Sanchez and Gavela, 2004).

Gastrointestinal complications: Human caliciviruses have emerged as a leading cause of acute diarrhea worldwide. In a study on the importance of calicivirus infections in HIV-related diarrhea, Rodriguez-Guillen *et al.* (2005) have shown that caliciviruses may be an important pathogen in children infected with HIV that cause diarrhea.

Bone marrow abnormalities: The abnormalities of the bone marrow include erythroid dysplasia, abnormal granulocytic, megakaryocytic development, cytopenia and anemia. The plasma cells are increased in number (Tripathi *et al*., 2005). These abnormalities are often observed at different stages of the disease. Adetifa *et al.* (2006) found both the main hematological disturbances (including the bone marrow abnormalities) and peripheral cytopenias in the HIVinfected children. Both the erythroid and other cell lines are affected by HIV/AIDS and other associated factors.

Malignancies and HIV infection: HIV patients are at increasing risk of developing cancer, particularly in the latter stages of AIDS. The infection and the adverse effects of the anti-retroviral therapy are known to predispose patients to AIDS-related malignancies, such as, such as Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin lymphoma, solid tumors and lung cancer (Cheung *et al*., 2005). These malignancies are the major causes of morbidity and mortality in AIDS patients. In addition, lymphepithelial parotid lesions are also frequently reported in vertically HIV-infected children (Rosso *et al*., 2006).

Mortality: Childhood HIV-related deaths appeared to be a major challenge to the health system. HIV/AIDS was estimated as the single largest cause of death in children of rural South Africa. In a study (1999-2003) on deaths at a Children's Hospital, Cape Town, Grandin *et al*. (2006) reported that 31.6% of the total 1978 deaths were due to HIV/AIDS in children. The study showed that female children were at higher risk of death. The mortality ratios in HIV infected children in rural South Africa have been described to be 59.6 deaths per 1000 live births for infants and 97.1 for children under 5 years of age. HIV/AIDS was attributed to 41% of the deaths in the under-5 age group, with a mortality rate of 8.6 per 1000 person-years. Lower respiratory infections caused an estimated 24.9 deaths per 1000 person-years in children under 1 year of age (Garrib *et al*., 2006). Ugochukwu (2006) found that HIV-related mortality was not gender-specific and was highest among infants.

PREVENTION

Routine screening, breast feeding and use of elective cesarean: Recent scientific developments have led to feasible and effective interventions to reduce the risk of mother to child transmission of HIV. Estimates of the number of perinatal HIV infections peaked in 1991 at 1,650 and declined to an estimated range of 144-236 in 2002 in the United States (MMWR, 2006). This reduction was attributed to routine HIV screening of pregnant women, avoidance of breastfeeding and use of elective cesarean delivery when appropriate. In a study (1982-1999) on 204 children born to 162 HIV-infected women, McDonald *et al*. (2001) found that elective caesarean delivery and avoidance of breastfeeding have been effective interventions for reducing the risk of mother-to-child HIV transmission in Australia.

The HIV/AIDS-pandemic causes many problems for the most affected societies and their health care systems. One of these is the 'Parent To Child Transmission' (PTCT) through breast milk and its prevention. The WHO advised HIV-infected women in developed countries to use alternatives to breastfeeding together with Highly Active Antiretroviral Therapy (HAAT) and optimal management of delivery to prevent transmission of HIV to their infants (Giles and Mijch, 2005). However, as economic and hygienic conditions do not always assure safe replacement of feeding in developing countries, a

WHO/UNAIDS/UNICEF-expert panel proposed methods to reduce the risk of PTCT but to use breastmilk for infant feeding (Yeo *et al*., 2005).

PROPHYLAXIS

With increased availability of antiretroviral therapy, there is an escalating global trend to test all pregnant women for HIV in order to stop perinatal transmission by use of antiretroviral drugs for treatment and prophylaxis (MMWR, 2006). During pregnancy, vaginal douche with chlorhexidine is considered for cases, where the membranes have ruptured more than 4 h previously. In addition a single dose of nevirapine is given to prevent the HIV disease. Cotrimoxazol is considered to prevent the opportune infections (Van Dillen *et al*., 2006). The vertical transmission of HIV has become the main target of prophylactic Zidovudina (AZT) therapy during gestation, parturition as well as for the newborn. Aggressive prophylactic measures of chemotherapy are given during pregnancy and or after birth to reduce the vertical transmission of HIV in different countries (Brazil, Cuba, Netherlands) and the results showed tremendous decline in the incidence of vertical transmission. The drugs used mostly are Zidovudine, lamivudine or a combination (Van Dillen *et al*., 2006). In Abidjan, peripartum exposure to Zidovudine is found to exert a protective effect for atleast 8 months (Dabis *et al*., 2001). Tarwireyi (2004) found Nevirapind treatment to HIV positive women (Antenatal care center, Zimbabwe) was found to reduce the rate of transmission of HIV by 50%.

A vaccine to protect HIV-exposed infants is an important goal to fight against the pandemic. Dickover *et al*. (2006) reported that maternal autologous neutralizing antibody can exert powerful protective and selective effects in perinatal HIV transmission and therefore has important implications for vaccine development. Two major challenges in pediatric HIV vaccine design are the competence of the neonatal/infant immune system in comparison to the adult immune system and the frequent exposure to HIV via breast-feeding. Thus, although infant macaques can respond quickly to oral viral challenge, the locally elicited immune responses at mucosal entry sites are likely to favor immune activation and thereby virus replication are insufficient to limit (Abel *et al*., 2006). An effective HIV-1 vaccine coupled with either passive immunization or short-term antiretroviral prophylaxis represents a potential strategy to prevent breast milk transmission (McFarland *et al*., 2006). In a recent study, Gray *et al*. (2007) suggested that the target to prevention of transmission, through breast feeding, may include the use of vaccination and/or passive immunization with neutralizing monoclonal antibodies.

Use of minerals, vitamins and antioxidants: The use of unproven dietary strategies, particularly vitamin and mineral supplements, is extremely popular in patients with HIV infection. This is because the deficiency of these supplements in the body is known to promote disease progression. For example, low selenium status may increase risk of mother-to-child transmission of HIV and poor pregnancy outcomes (low birthweight, small for gestational age, preterm birth and fetal death). Similarly, low GSH levels are shown to promote HIV expression and impair T cell function in both in vitro and clinical studies (Leonore *et al*., 1997). The multivitamin supplements and different antioxidants, including selenium and glutathione are essential for viability and function of virtually all cells (Kupka *et al*., 2005).

TREATMENT STRATEGIES FOR HIV INFECTION

HIV is a member of the lentivirus group of Retroviridae and hence, most of the antiretroviral drugs are directed against viral replication. In a report on 188 cases from Egypt, Elhaggar (1993) reported that Zidovudine, dideoxinosine, didanosine, dideoxcytidine and phosphonic acid esters were found to improve the median survival of AIDS patients from 11 months (1985) to 18-25 months (1991). AZT was found to increase the median survival of AIDS patients from 9.6 months in the untreated to 21.2 months in the treated. In developing countries like India, drugs like zidovudine, lamivudine, stavudine, nevirapine and indinavir are available and are used in symptomatic patients (Kaul and Patel, 2001). In studies on treatment modalities of pediatric HIV infections, Ziegler and Palasanthiran (1997) reported that AZT antiviral monotherapy was not appropriate and during late 90s, the antiretroviral therapy with a combination of two or three drugs including AZT plus didanosine or lamivudine in addition to protease inhibitor was practiced. Enfuvirtide, is also one of the approved drugs, but it can be injected by subcutaneous injection only (Fatkenheuer, 2005). The CCR5 antagonists represent a group of experimental medications, whose use is conceivable at all stages of the HIV infection. Literature reports suggest that they are effective and also very well tolerated and, therefore are one of the most promising future classes of drugs (Fatkenheuer, 2005). Recently, nucleoside reverse transcriptase inhibitors (abacavir/lamivudine/zidovudine plus tenofovir) have

been investigated in both antiretroviral-naïve patients and in heavily pre-treated patients, as well in the setting of simplification/switching strategies. This experimental combination was found to be safe and attractive option with advantages of limited toxicity, few drug interactions (Mastroianni *et al*., 2006). Suksomboon *et al.* (2007) reported Zidovudine alone or in combination with lamivudine and nevirapine monotherapy is effective for the prevention of mother-to-child transmission of HIV. These drugs may also be beneficial in reducing the risk of infant deaths.

In recent years, non-coding nucleic acids have emerged as potent inhibitors that dramatically suppress viral function both in vitro and in cell culture. In particular, the RNA and DNA aptamers inhibit HIV function by directly interfering with essential proteins at critical stages in the replication cycle. Their antiviral efficacy is expected to be a function, in part, of the biochemical properties of the aptamer-target interaction. The modern trends of the treatment strategies include inhibition of virus enzymes (reverse transcription, proteolytic processing and chromosomal integration), viral expression (Rev/RRE and Tat/TAR), viral packaging (P55 Gag, matrix and nucleocapsid) and viral entry (gp120). Additional nucleic acid-based strategies for inactivation of HIV function (including RNAi, antisense and ribozymes) have also demonstrated their utility (Santoro *et al*., 2006; Held *et al*., 2006). Although developments in small molecule therapeutics for HIV have been dramatic, RNA interference (RNAi) is a process in which double-stranded RNA triggers the silencing of gene expression in a sequence-specific manner. RNAi has been found to interfere with different stages of HIV replication (Nekhai and Jerebtsova, 2006). For salvage therapy of HIV-infected patients, new and potent drugs are needed. The protease inhibitors (Tipranavir and TMC114) have a high potency against multidrug-resistant viral strains and are the most promising drugs for the near future. Substances in the groups of integrase and maturation inhibitors are in the primitive stages of clinical development (Arasteh and Muller, 2005). In the recent years, the development of vaginal microbicides for the prevention and treatment of sexual transmission of HIV is becoming an increasingly important strategy against AIDS (Tien *et al*., 2005).

TREATMENT FOR CO-MORBIDITY

Effect of drugs developed for HIV treatment against Severe Acute Respiratory Syndrome (SARS) include protease inhibitors (lopinavir/ritonavir) that have been reported to be promising. Antibiotic prophylaxis and use of Cotrimoxazole (CTM) was considered a positive treatment of HIV infected Zambian children, having respiratory tract infections, recurrent severe bacterial infections and oral candidiasis (Walker *et al*., 2006). Courtsoudis *et al*. (2005) found that CTM prophylaxis is protective against lower respiratory tract infections in HIV-infected children. However, because of a possible association between CTM prophylaxis and an increased risk of diarrhoea, HIV status of infants should be determined as early as possible in order to prevent unnecessary exposure of uninfected infants to CTM prophylaxis. The treatment of tuberculosis includes drugs such as isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin (API Consensus Expert Committee, 2006).

The hepatitis flares may be followed by normalization of ALT and clearance of Hepatitis B Virus (HBV) DNA. If lamivudine is included in the HAART regime, hepatitis flares may not occur till late and these late flares signal the development of lamivudine resistance. Treatment options for chronic HBV infection include Interferon (IFN) and nucleoside analogues. Lamivudine, adeflovir dipivoxil, tenofovir disoproxil fumarate are nucleoside analogues with activity against both HBV-DNA polymerase and HIV reverse transcriptase (Guan, 2005).

Thrombocytopenia in HIV patients represents a risk for bleeding which is further deleterious during surgery. The accelerated peripheral platelet destruction of platelets from the infected megakaryocytes can be averted by therapeutic infusion of HIV infected patients with pegylated recombinant human megakaryocyte growth development factor, which can restore platelet counts to normal levels (Sundell and Koka, 2006). Treatment decisions for AIDS-related Kaposi's Sarcoma (KS) are guided largely by the presence and extent of symptomatic disease. In addition to HAART, excellent treatments, such as; topic gel, radiotherapy and intralesional therapy and advanced therapeutic solutions (liposomal anthracyclines, paclitaxel) are available. Novel therapies that have become available to treat AIDS-related KS include angiogenesis inhibitors and antiviral agents (Cheung *et al*., 2005).

In a study of 2 formulations of recombinant canarypox ALVAC vaccine (vCP205) against Human Immunodeficiency Virus type 1 (HIV), Johnson *et al.* (2005) found vCP205 to be safe and immunogenic. HIV-infected pediatric patients are known to often suffer with neuropathic pain and painful spasticity. The suitable treatment for this is the use of antidepressants and anticonvulsants. The spasticity can be reduced with myorelaxnts. Children are often responsible to behavioral methods such as relaxation, hypnosis and or distraction (Dollfus, 1997).

TOXICITY OF DRUGS

Although HAAT has been effective in reducing the mortality and morbidity in recent years, adverse side effects of the chemotherapy, patient non-compliance and the development of viral resistance remain major problems. Literature reports underline that the prevalence of HIV associated neurological diseases are reported to be increased after the introduction of active antiretroviral therapy. There was a rise observed in diseases like encephalo- and myelopathy and polyneuropathy (Arendt, 2005). The antiretroviral drugs are reported to cause lipid abnormalities and vascular complications in HIV-infected population (Monforte and Bongiovanni, 2005). These drugs are found to cause body weight gain and lipodystrophy, leading to obstructive sleep apnoea. Common symptoms during day time were somnolence, fatigue and snoring (Lo *et al*., 2006). Co-infection with hepatitis C virus and HIV is a known risk factor for hepatotoxicity in patients receiving HAAT. It is known to cause liver fibrosis associated with hepatotoxicity (Aranzabal *et al*., 2005). Guan (2005) found that new and improved agents in the HAAT continue to prolong survival, but the use of liver transplantation for cirrhotic patients co-infected with HIV and hepatitis B virus may increase. The author found anti-retroviral agents to be hepatotoxic and cause ALT elevations in patients with chronic hepatitis. Furthermore, Lamivudine, was observed to be the initial treatment of hepatitis B and also the root cause of high incidence of resistance in the virus. The hepatotoxicity of many HIV therapies and the possible negative impact of Hepatitis C Virus (HCV) on this treatment, alongside the interactions and contraindications of many HIV and HCV therapies, further limits the choice of paediatric treatments for coinfected children (England *et al*., 2006). The use of antiretroviral therapy is also known to cause kidney disease among the patients (Sanchez and Gavela, 2004). Among the anti-tuberculosis drugs, streptomycin is not given during pregnancy, as it is known to cause ototoxicity to the fetus (API Consensus Expert Committee, 2006). In neonates, Zidovudine is reported to cause mitochondrial DNA depletion and has been implicated in the development of severe lactic acidosis and multiorgan failure. The antiretroviral drugs have been associated with low neutrophil accounts. In a recent study (Wells *et al*., 2006), nevirapine prophylaxis given for 6 months in breast-feeding Zimbabwean infants was found to cause neutropenia in several cases. Zidovudine-based antiretroviral therapies for treatment of HIV-infected pregnant women have markedly reduced mother-to-child transmission of HIV. Nevertheless, these drugs have been found to induce chromosomal damage, gene mutations, micronuclei and cancers in animals, following direct or transplacental exposure (Witt *et al*., 2007). Thus, the advances in the treatment strategies, may lead to morbidity and mortality due to cancers. Most common malignancies related with AIDS have been reported to be Kaposi's sarcoma, Hodgkin's and non-Hodgkin's lymphomas (Cheung *et al*., 2005). The HIV vaccines coupled with either passive immunization or short-term antiretroviral prophylaxis was found to cause mild to moderate local reactions, however; no significant systematic toxicities were observed (McFarland *et al*., 2006). In some infants HIV-1-specific proliferative and antibody responses were found to persist until week 104. Furthermore, these authors detected HIV-specific cytotoxic T lymphocyte responses in some subjects. However, the frequency of HIV specific cytotoxic T lymphocyte responses did not differ between vaccine and placebo recipients. These authors suggested that an effective HIV vaccine coupled with either passive immunization or short-term antiretroviral prophylaxis would represent a potential strategy to prevent breast milk transmission.

CONCLUSION

Literature reports suggest that prevention of HIV/AIDS by support programs (educational and socio-economical) are still the most desired strategy. These measures have given place for many issues which are vital for a parallel development along with progress on the scientific arena. Nevertheless, the population statistics of HIV-infected children, according to the latest WHO figures, shows that despite of the tremendous efforts, world-wide, we are still not able to control the global epidemic of HIV. Hence, there is an imperative need for more active research on development of novel prophylactic agents, development of vaccines, newer therapeutic options (both synthetic and natural) and gene therapy to control the disease.

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