

Review Articles

HIV/AIDS in Children: Current Update

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Abstract

Human immune deficiency virus (HIV) infection leading to acquired immune deficiency syndrome (AIDS) has been a major cause of illness and death among children, teens and young adults worldwide. In recent years, HIV infection rates have been increasing rapidly among teens and young adults. The three main ways HIV is passed to a very young child are: intrauterine, at the time of birth and during breast feeding. Among the teens, the virus is most commonly spread through unprotected sex, sharing needles or in very rare cases by direct contact with an open wound of an infected person or through blood transfusion. A baby born with HIV infection most likely will appear healthy. But within 2 to 3 months after birth, an infected baby might begin to appear sick, with poor weight gain, repeated infections, and enlargement of lymph nodes, liver or spleen and neurological problems. Every pregnant woman should be tested for HIV to have a better chance of preventing transmission to her unborn child. Older kids, teens and adults are tested for HIV infection and if found positive should undergo protocolized treatment. There is no vaccine to prevent HIV and AIDS although researchers are working to develop one. Thus, prevention of HIV remains of worldwide importance.

Key words: HIV, AIDS, treatment, prevention.

Background

Acquired immune deficiency syndrome (AIDS) was first recognized by the United States Center for Disease Control (CDC) and Prevention in 1981 and its cause - Human immune deficiency virus (HIV) infection - was identified in the early part of the decade.¹ Genetic research indicates that HIV originated in the West - Central Africa during the late ninetieth or early twentieth century.² Since its discovery, AIDS has caused an estimated 36 million deaths worldwide. As of 2012, approximately 35.5 million people are living with HIV globally.³ HIV/AIDS is considered a pandemic - a disease outbreak which is present over a large area and is actively spreading. HIV/AIDS has had a great impact on society, both as an illness and a source of discrimination. The disease also has significant economic impact. There are many misconceptions about it such as the belief that it can be transmitted by casual non-sexual contact. The disease has also become subject to many

controversies involving religion. It has attracted medical and political attention as well as large scale funding since it was identified in the 1980s.⁴

Since the first cases of HIV infection were identified, the number of children infected with HIV has risen dramatically in developing countries, the result of an increased number of HIV-infected women of child bearing age in these areas. Globally, between 2002 and 2013, there was a 58 percent reduction in the number of new HIV infection. Despite this, more than 240,000 children were infected with HIV during 2013. The figure below shows the number of children (defined by UNAIDS as under 15 years of age) directly affected⁵:

- 3.2 million children living with HIV around the world at the end of 2013.
- 240,000 children become newly infected with HIV in 2013.
- 58 percent drop in new infections since 2002, and a 43 percent drop in 2007.
- 91 percent of children living with HIV live in sub-Saharan Africa.
- 24 percent of children needing antiretroviral treatment received in 2013.

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- 190,000 children died of AIDS - related illness during 2013, out of 1.5 million people overall.

The first case of HIV in Bangladesh was detected in 1989 and it is estimated that 6200 people have been infected with HIV by the end of 2009. An estimated 1400 were newly infected in 2009. In December 2010, the Ministry of Health and Family Welfare had confirmed 2088 cases of HIV among which 800 had developed AIDS and 211 had died.^{6,7} Of note is the rapid increase in prevalence among women. In 2001, only 1.3 percent of all HIV infections had occurred among women while in 2007 nearly 17 percent were women. In 2004, the National AIDS/STD program estimated that 2.2 to 3.9 million people were at risk of infection, most of whom were intravenous drug Users (IDUs), female and male sex workers and their clients, and external migrant workers. The key risk factors in Bangladesh are large commercial sex industries, low levels of condom use, needle sharing among IDUs, a high number of migrants and a low level of knowledge about HIV and AIDS among general population. High levels of stigmata prevent effective prevention and mitigation of HIV.⁸

Definition

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a disease spectrum of the human immune system caused by infection with human immunodeficiency virus (HIV).⁹ The term HIV/AIDS represents the entire range of the effects of infection which range from an often asymptomatic post infection stage to full-blown AIDS, with an array of opportunistic infections.¹⁰

Etiopathogenesis

HIV is the cause of the spectrum of disease known as HIV/AIDS. HIV is a retrovirus that primarily infects components of the human immune system such as the CD4+ T cells, macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells.¹¹ HIV is a member of the genus Lentivirus,¹² which is transmitted as single stranded, positive-sense, enveloped virus. Upon entry into the target cells, the viral genome is converted (reverse transcribed) into double stranded DNA by a virally encoded reverse transcriptase. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors.¹³ Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system.¹⁴ Alternatively, the

virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.¹⁵ Two types of HIV have been characterized: HIV-1 and HIV-2. HIV -1 is the virus that was originally discovered. It is more virulent, infective, and is the cause of the majority of HIV infections globally.¹⁶

After the virus enters the body, there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.¹⁷ This response is accompanied by a marked drop in the number of circulating CD4+ T cells. The acute viremia is almost invariably associated with activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion.¹⁸ Ultimately, HIV causes AIDS by depleting CD4+ T cells. This weakens the immune system and allows opportunistic infections.¹⁹ Although the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of CD4+ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbors the majority of the lymphocytes found in the body.²⁰ A vigorous immune response eventually controls the infection and initiates the clinically latent phase. CD4+ T cells in mucosal tissue remain particularly affected.²¹ Continuous HIV replication causes a state of generalized immune activation which is reflected by the increased activation state of immune cells and release of proinflammatory cytokines.²²

Transmission

HIV is transmitted by three main routes: sexual contact, exposure to infected body fluids of tissues, and from mother to child during pregnancy, delivery or breast feeding (known as vertical transmission).²³ There is no risk of acquiring HIV if exposed to feces, nasal secretions, saliva, sputum, sweat, tears, urine or vomitus unless they are contaminated with blood.²⁴ The viral load of an infected person is an important risk factor in both sexual and mother-to-child transmission.²⁵ In the absence of treatment, the risk of transmission before or during birth is around 20% and in those who also breastfed 35%. As of 2008, vertical transmission accounted for about 90% of cases of HIV in children. With appropriate treatment, the risk of mother-to-child infection can be reduced to about 10%.²⁶

Classifications/Types

Although most HIV-1 infected individuals have a detectable viral load and in the absence of treatment will eventually progress to AIDS, a small proportion (about 5%) retain high levels of CD4+ T cells without antiretroviral therapy for more than 5 years. These individuals are classified as HIV controllers or long term non-progressors.²⁷ Another group is those who also maintain a low or undetectable viral load, without antiretroviral treatment who are known as “elite controllers” or “elite suppressors”. They represent approximately 1 in 300 infected persons.²⁸

Clinical features

There are three main stages of HIV infection: acute infection, clinical latency and AIDS.²⁹

- Acute infection** is the initial period following the contraction of HIV, also known as primary HIV or acute retroviral syndrome.³⁰ Many individuals develop an influenza like illness or a mononucleosis-like illness 2-4 weeks post exposure while others have no significant symptoms.³¹ Symptoms occur in 40-90% of cases and most commonly include fever, large tender lymph nodes, throat inflammation, a rash, headache, and/or sores of the mouth and genitalias.³² Some people also develop opportunistic infections at this stage.³³ Gastro-intestinal symptoms such as nausea, vomiting or peripheral neuropathy or Guillain-Barré syndrome. Due to their non-specific character, these symptoms are not often recognized as signs of HIV infection. Thus, it is recommended that HIV be considered in people presenting an unexplained fever, who may have risk factors for the infection.³⁴
- Clinical latency:** The initial symptoms are followed by a stage called clinical latency, asymptomatic HIV or chronic HIV.³⁵ Without treatment, this second stage of the natural history of HIV infection can last from about three years to over 20 years (on average about 20 years). While typically there are few or no symptoms at first, near the end of this stage, many people experience fever, weight loss, GI problems and muscle pains. Between 50 and 70% people also develop persistent generalized lymphadenopathy, characterized by unexplained, non-painful enlargement of more than one group of lymph nodes (other than groin) for over 3 to 6 months.³⁶
- Acquired immunodeficiency syndrome (AIDS):** AIDS is defined in terms of either a CD4+ T cell count below 200 cells/μl or the occurrence of specific diseases in association with an HIV infection. In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%), cachexia in the form of HIV wasting syndrome (20%) and esophageal candidiasis. Other common signs include recurring respiratory tract infections. Opportunistic infections may be caused by bacteria, viruses, fungi and parasites that are normally controlled by immune system. These infections may affect nearly every organ system.³⁷ People with AIDS have an increased risk of developing various viral induced cancer including Kaposi's sarcoma, Burkitt's lymphoma, primary CNS lymphoma and cervical cancer.³⁸ Additionally, people with AIDS frequently have systemic symptoms such as prolonged fever, sweats (particularly at night), swollen lymph nodes, chills, weakness and weight loss.³⁹ Diarrhoea is another common symptom present in about 90% people with AIDS.⁴⁰ They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers.⁴¹

Progression of HIV Diseases in Children

Researchers have observed two general patterns of illness in HIV-infected children. About 20% of children develop serious disease in the first year of life; most of these children die by the age of 4 years. The remaining 80% infected children have a slower rate of disease progression, many not developing the most serious symptoms of AIDS until school entry or even adolescence.

Diagnosis

HIV infection is often difficult to diagnose in very young children. Infected babies, especially in the first few months of life, often appear normal and may exhibit no telltale signs that would allow a definitive diagnosis of HIV infection. Moreover, all children born to infected mothers have antibodies to HIV, made by the mother's immune system, that cross the placenta to the baby's blood stream before birth and persist up to 18 months. Because these maternal antibodies reflect the mother's but not the infant's infection status, the test

is not useful in newborns or young infants. In recent years, investigators have demonstrated the utility of highly accurate blood tests in diagnosing HIV infection in children 6 months of age and younger. One laboratory technique called polymerase chain reaction (PCR) can detect minute quantities of the virus in an infant's blood. Another procedure allows physicians to culture a sample of an infant's blood and test it for the presence of HIV. Currently, PCR or HIV culture techniques can identify at birth about one-third of infants who are truly HIV-infected. With these techniques, approximately 90 percent of HIV-infected infants are identified by 2 months of age, and 95 percent by 3 months of age. One innovative new approach to both RNA and DNA PCR testing uses dried blood spot specimen, which should make it much simpler to gather and store specimens in field setting. In older children and adults, an ELISA to detect HIV antibody followed by a confirmatory Western Blot (which has increased specificity), should be used to diagnose HIV infection.⁴²

Management

There is currently no cure or effective HIV vaccine. The National Strategic Plan of Bangladesh for HIV/AIDS includes Pediatric HIV as an integrated part of care, support and treatment (CST). Coordination of Pediatric HIV CST is integrated with the HIV care and treatment group. Currently, there are 16 drug products approved by the FDA for the treatment of adult HIV infection. Ten antiretroviral agents have pediatric label information, including 3 protease inhibitors. While the basic principles that guide treatment of pediatric HIV infection are the same as for any HIV-infected person, there are a number of unique scientific and medical concerns that are important to consider in the treatment of children with HIV infection. These range from differences from adults in age-related issues such as CD4 lymphocyte counts and drug metabolism to requirements for special formulation and treatment regimens that are appropriate for infants through adolescents. As in adults, treatment of HIV-infected children today is complex task of using potent combinations of antiretroviral agents to maximally suppress viral replication. Long term assessment of these children is also a high priority to assess sustained antiretroviral benefits as well as to monitor for potential adverse consequences of treatment⁴³. Drug to treat HIV/AIDS use several different strategies, including:

- interfering with HIV's reproduction of its genetic material (called nucleoside or nucleotide antiretroviral).
- interfering with the enzymes HIV needs to take over certain body cells (protease inhibitors).
- interfering with HIV's ability to pack its genetic materials into viral code (non-nucleoside reverse transcriptase inhibitors, NNRTIS).
- newer types of medications (integrase inhibitors and CCR5 inhibitors) that use different strategies.

Because these drugs work in different ways, doctors generally prescribe a "combination cocktail" of these drugs that is taken everyday. Doctors also prescribe drugs to prevent certain opportunistic infections. Once treatment is begun, it is recommended that it is continued without breaks or holidays. The desired outcome of treatment is a long term plasma HIV-RNA count below 50 copies/ml.

Treatment consists of high active antiretroviral therapy (HAART) which slows progression of the disease.⁴⁴ Current HAART options are combinations consisting of at least three medications belonging to at least two types, or "classes" of antiretroviral agents.³⁸ Initially, treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analogue reverse transcriptase inhibitors (NRTIS).⁴⁵ Treatment recommendations for children are somewhat different from those for adults. The WHO recommends treating all children less than 5 years of age; children above 5 are treated like adults.⁴⁶ Measures to prevent opportunistic infections are effective in many people with HIV/AIDS. In addition to improving current disease, treatment with antiretroviral reduces the risk of developing additional opportunistic infections.⁴⁷ With respect to dietary advice and AIDS, some evidence has shown a benefit from micronutrient supplements. There is some evidence that vitamin A supplementation in children reduces mortality and improves growth.⁴⁸

Prognosis

HIV/AIDS has become a chronic rather than an acutely fatal disease in many areas of the world.⁴⁹ Prognosis varies between people, and both the CD4 count and viral load are useful for predicted outcome. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype. After the diagnosis of AIDS, if treatment is not available, survival ranges between 6

and 19 months.⁵⁰ Half of the infants born with HIV die before two years of age without treatment. The primary causes of death from HIV/AIDS are opportunistic infections and cancer, both of which are frequently the results of the progressive failure of the immune system. Risk of cancer appears to increase once the CD4 count is below 500/ μ l. Tuberculosis co-infection is one of leading causes of sickness and death with HIV/AIDS being present in a third of all HIV infected people and causes 25% of all HIV related deaths. HIV is also one of the most important risk factors for tuberculosis.⁵¹ Hepatitis C is another very common co-infection where each disease increase the progression of the other.⁵² The two most common cancers associated with HIV/AIDS are Kaposi's Sarcoma and AIDS-related non-Hodgkin's lymphoma.⁵³ Even with antiretroviral treatment, over the long term HIV-infected people may experience neurocognitive disorders, osteoporosis, neuropathy, cancers, nephropathy and cardiovascular disease. It is not clear whether these conditions result from the HIV infection itself or are adverse effects of treatment.⁵⁴

Prevention

There is no effective vaccine for HIV or AIDS. Comprehensive sexual education provided at school may decrease high risk behavior.⁵⁵ Treating people with HIV whose CD4 count >350 cells/ μ L with antiretroviral protects >96% of their partners from infection. Universal precautions within the health care environment are believed to be effective in decreasing the risk of HIV.⁵⁶ A course of antiretroviral administered within 48 to 72 hours after exposure to HIV-positive blood or genital secretions is referred to as post-exposure prophylaxis. As of 2013, the prevention regimen recommended in the United States consists of three medications - tenofovir, conicitabine and raltegravir - as this may reduce the risk further. The duration of treatment is usually four weeks. The use of the single agent ziduvudine reduces the risk of a HIV infection five fold - following a needle stick injury.⁵⁷

Bangladesh responded early and decisively to the potential threat of HIV. In 1985, the Government of the Peoples Republic of Bangladesh established the National AIDS Committee (NAC) and mandated it to coordinate the response. In June 2010, the National strategic plan (NASP) established a steering committee to oversee the development of the NASP for HIV/AIDS 2011-2015. The goal set by the

committee is to minimize the impact of AIDS on the individual, family, community and society. Of the strategies, the important one was to preventing Mother-to-Child Transmission (PMTCT) of HIV6. UNAIDS⁵⁸ advocate for key strategies for preventing mother-to child transmission:

- keeping women of reproductive age and their partners HIV-negative through reproductive health and HIV prevention services.
- avoiding unwanted pregnancies among HIV-infected women and women at risk of HIV, through family planning and HIV testing and counselling services.
- ensuring HIV testing of pregnant women and timely access to effective antiretroviral therapy, both for the health of HIV-infected mothers, and for PMTCT, during delivery and breast feeding.
- better integration of HIV care, treatment and support for HIV-infected women and their families.

When an HIV-infected women is found to be pregnant, the following treatment plan to be implemented:⁵⁸

- before the birth of her baby: antiviral treatments given to the mother during pregnancy can help prevent HIV transmission to the baby.
- at the time of birth: antiviral medications can be given to both the mother and the newborn to lower the risk of HIV transmission that can occur during the birth process; in addition, the mother will be encouraged to formula-feed rather than the breast feed, because HIV can be transmitted to her baby through breast milk.
- during breast feeding: because breast feeding is discouraged among HIV-infected mothers, in places in the world with limited access to formula or clean water supply to mix it, both the mother and the child can be treated with medications to lower the baby's risk of HIV infection.

When a child is born to a HIV-infected mother the following steps to be taken to prevent PMTCT:⁶

- immediately after birth, neonates should get single dose of NVP within 72 hours of birth and AZT two times daily for 1-4 weeks, depending whether the mother took ART during pregnancy or not
- at 6 hours of age: all exposed babies should start taking CTX, this is the same drug that adults take to prevent pneumonia.

- ongoing: if the baby is HIV- infected, a CD4 test needs to be done; CD4% is a better measure in children under 5 years of age; babies should keep taking CTX until it is definite that they are not HIV-infected and they no longer breast feeding.

Programs to prevent the vertical transmission of HIV (from mothers to children) can reduce the rates of transmission by 92-99%. This primarily involves the use of a combination of antiviral medications during pregnancy and after birth in the infant and potentially includes bottle feeding rather breastfeeding.⁵²

Conclusion

HIV/AIDS is a global pandemic. The transmission of HIV from mothers to their infants contribute substantially to global morbidity and mortality for children under-5 years of age. HIV infection is often difficult to diagnose in very young children. Prevention of HIV infection remains of worldwide importance. It is vital that children who were infected via mother-to-child transmission receive treatment to keep them healthy. Cases of HIV infection and AIDS in children are complicated and should be managed by experienced health care professionals. It is also of utmost importance to do routine HIV testing and counselling of all pregnant woman.

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