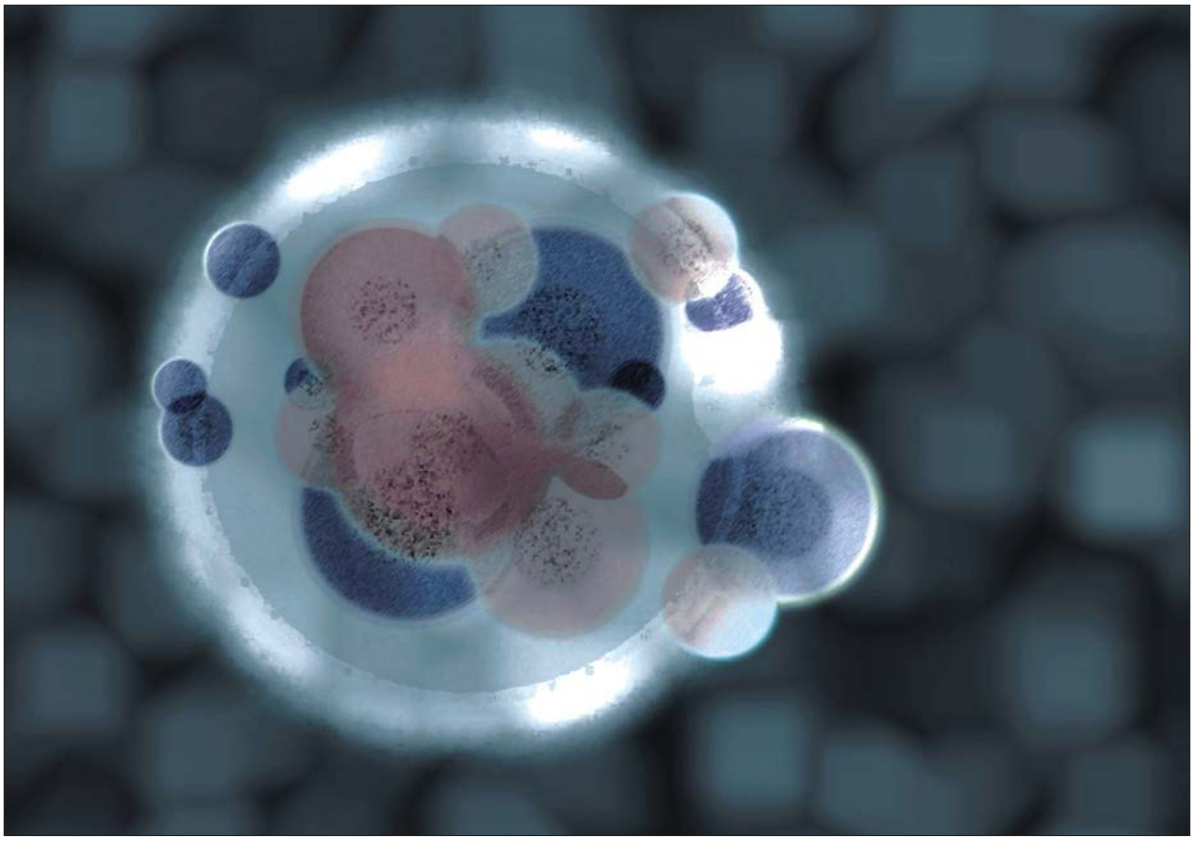

Journal of Biological Sciences

ISSN 1727-3048

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Journal of Biological Sciences 7 (8): 1296-1304, 2007
ISSN 1727-3048

A Review of the Epidemiology, Biology and Pathogenesis of HIV

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Abstract: The HIV/AIDS epidemic continues to have a devastating effect on people in Africa especially those in the Sub-Saharan Africa. Over 34 million people living in Sub-Saharan Africa had been infected with HIV with more than 12 million of these already dead. It has been shown from the natural history of HIV infection that it is usually lethal to those infected by it. Factors suggested to affect the duration of clinical history include genetic susceptibility, viral load, concurrent infections and pre-existing immune status at the time of HIV infection. Based on available data, the survival time of HIV-infected persons is much shorter in Africa than in those in western countries. Many of the persons infected in Africa have poor access to a health care system; other infections such as tuberculosis combined with poverty and malnutrition seem to be playing important roles in the epidemiology and pathogenesis of HIV. In this study, the epidemiology, the biology and pathogenesis of HIV is examined.

Key words: Epidemiology, biology, pathogenesis, human immunodeficiency virus, acquired immune deficiency syndrome

INTRODUCTION

The Human Immunodeficiency Virus (HIV) is seen as one of the most severe infections ever known to have attacked the human population, especially the economically productive age group between 15-49 years (UNAIDS, 2001). HIV is also seen as an infection of attitude and behaviour, as it is closely associated with sexual behaviour, especially where a person has more than one sexual partner (UNAIDS, 2000, 2001; Oguntibeju and Fabode, 2002; ADSA, 1996; Dhlanraj, 2000; Dannhauser *et al*., 1999; Dorrington *et al*., 2001). Scientific evidence has shown that HIV infection is caused by a retrovirus named the HIV. HIV is a ribonucleic acid (RNA) retrovirus, so designated because of its genome that encodes an unusual enzyme called reverse transcriptase. This enzyme allows deoxyribonucleic acid (DNA) to be transcribed from RNA. Thus, HIV can make copies of its own genome as DNA in the host's cells, such as human T4-helper lymphocytes and this leads to the elaboration of vast numbers of viral particles (Weiss, 1996; Denny *et al*., 1998; Oguntibeju and Banjoko, 2003). There has been a drastic increase in the number of people infected with HIV, in spite of various efforts made to combat this infection. This increase is not peculiar to a particular racial group, country and community. It is a worldwide problem. However, according to reports, the greatest incidence of HIV infection is found in Sub-Saharan Africa (UNAIDS, 2001; SAHIVCS, 2001).

Definition of AIDS: The acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus named the HIV which selectively attacks and depletes T-lymphocytes bearing the CD4 receptor (T-helper cells), causing a predisposition to opportunistic infections and malignancies (Sabatier, 1987; Weiss, 1996; Wong *et al*., 1997). In its definition, the World Health Organization (WHO) gave a provisional clinical case definition for AIDS in places where diagnostic resources are limited and stated thus:

AIDS in adults: This is defined by the existence of at least two of the major clinical signs associated with at least one minor clinical sign in the absence of known causes of immuno-suppression such as cancer or severe malnutrition, or other recognised aetiologies. The major clinical signs include weight loss of more than 10% of the body weight, chronic diarrhoea for more than one month and prolonged fever for longer than one month. The minor signs are generalized lymph-adenopathy, a persistent cough for longer than one month and oropharyngeal candidiasis. It also stated that the presence of generalized Kaposi's sarcoma or cryptococcal meningitis are

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sufficient clinical signs by themselves for the diagnosis of AIDS in the adult group (WHO, 1993; Barnhart *et al*., 1996; SAHIVCS, 2001).

AIDS in children: Paediatric AIDS should be suspected in an infant or a child presenting with at least two major clinical signs associated with at least two minor signs in the absence of known causes of immuno-suppression. The major clinical signs include weight loss or abnormally slow growth and chronic diarrhoea for longer than one month. The minor clinical signs include generalized lymph-adenopathy and oropharyngeal candidiasis (WHO, 1993; Barnhart *et al*., 1996; SAHIVCS, 2001).

Natural history of HIV infection: Observations have shown that from the natural history of the disease, it is usually lethal to those who are infected by HIV. Furthermore, every person infected is an active carrier of the virus to an unsuspecting contact, even before the infected carrier presents with AIDS. The mean time from infection with HIV to the development of AIDS is about nine to ten years in industrialized countries (Weiss, 1996; Liu *et al*., 2000). Factors that are suggested to affect the duration of clinical latency include genetic susceptibility, viral load, concurrent infections as well as the pre-existing immune status at the time of HIV infection (Royce *et al*., 1997). Based on available data, the survival time of HIV infected persons is much shorter in Africa than in industrialised countries (Enwonwu, 1992; Gilks, 1993; Piwoz and Preble, 2000; SAHIVCS, 2001).

Studies suggest a rapid transition from asymptomatic HIV infection to AIDS (Enwonwu, 1992; Bentwich *et al*., 1999; Hazenberg *et al*., 2000). Many of the patients in Africa have poor access to health care systems, therefore infections due to endemic pathogens such as *Mycobacterium tuberculosis*, *Streptococcus pneumonia* and non-typhoid salmonellae coupled with malnutrition seem to be playing a significant role in the cause of death (Gilks, 1993; Tindall and Copper, 1991; SAHIVCS, 2001).

Classification of HIV infection: In 1986, the United States Centers for Disease Control and Prevention (CDC) developed the first classification system for HIV infection with the focus on AIDS-defining opportunistic infections and malignancies (CDC, 1987). The CDC classification system was revised in 1987 to reflect clinical practice more practically and included in it the HIV wasting syndrome along with other HIV related diseases. The former classification refers to the presence of involuntary weight loss of greater than 10%, accompanied by chronic diarrhoea (>30 days) or documented fever (>30 days). In 1991, the classification of AIDS included all HIV-infected individuals with $CD4^+$ T-cell counts $<200\times10^6$ (Buehler *et al*., 1993; SAHIVCS, 2001). In 1993, the WHO staging system for HIV infection and disease was formulated as universal staging system for HIV infection with some flexibility for international use, including countries with limited access to technology. The WHO did not include pulmonary tuberculosis as an AIDS defining illness within this staging system, since it occurs as an endemic disease in many developing countries. Involuntary weight loss of greater than 10% of normal weight in clinical stage 3 and the HIV wasting syndrome in stage 4 were included (WHO, 1993; SAHIVCS, 2001). This staging is currently in use in South Africa and other African countries (Martin, 2000; SAHIVCS, 2001).

The epidemiology of HIV/AIDS

Origin and history of HIV/AIDS epidemic: The first reported cases of AIDS were recorded in the morbidity and mortality weekly report of June 5 1981, in the United States of America and concerned five young men, all active homosexuals who had been treated in Los Angeles hospital for a rare infection called *Pneumocystis carinii* pneumonia (PCP). All five men had evidence of other infections and a defective immune system. About the same period, physicians in the United States of America diagnosed Kaposi's sarcoma (an uncommon malignancy) in 26 homosexual men whose ages ranged from 26-51 years (Cahill, 1994; UNAIDS, 2000, 2001).

Global epidemiology of HIV infection and AIDS: The HIV/AIDS pandemic is perhaps the most serious disease threat to this generation. There is, however, inadequate information on the extent of its spread (UNAIDS, 2002). Reports show that global statistics are collated by WHO, but these statistics are usually incomplete because, for a number of reasons, many authorities do not/are unable or are unwilling to give an accurate figure regarding the number of cases occurring in their countries (Sabatier, 1987; SAHIVCS, 2001). The epidemiological data available on the distribution of HIV/AIDS cases throughout the world point to distinct patterns, each of which is characterized by the time the infection or disease was diagnosed and the predominant modes of transmission (Martin, 2000; UNAIDS, 2002).

At the end of 2001, an estimated 40 million people globally were documented to be living with HIV. In many parts of the developing world, the majority of new infections occur in young adults, with young women especially being more vulnerable. About one-third of those currently living with HIV/AIDS are between 15 and 49 years of age. Most of them do not know that they

are carrying the virus. Many people in Africa especially those living in the rural areas, know nothing or too little about HIV to protect themselves against the virus (UNAIDS, 2001; Oguntibeju *et al*., 2002).

The pattern of HIV/AIDS distribution has implications for the type of prevention and nutritional support needed and for the priority that needs to be given to different aspects of the activities that would reduce its spread and improve the health status of those already infected with HIV (UNAIDS, 2000).

Pattern 1: In pattern 1 areas, most cases of HIV infection and AIDS occur in homosexual or bisexual males and in intravenous drug users. Heterosexual transmission is also increasing, but it is responsible for only a small percentage of cases. This pattern is typical of North America. The male to female ratio of HIV/AIDS reported cases range from 10:1 to 15:1 (Royce *et al*., 1997; UNAIDS, 2001).

Pattern 2: This is typical of most Sub-Saharan Africa and parts of the Carribbean. Most of the reported cases in these regions occur through sexual transmission among heterosexuals with the male to female ratio of documented cases put at ratio 1:1. Transmission from intravenous drug users and homosexual relationship occurs at a lower rate than heterosexual transmission (Royce *et al*., 1997; UNAIDS, 2000).

Pattern 3: This pattern is found in North Africa, Eastern Europe, Asia and most parts of the Pacific. In these areas, HIV appears to have been introduced in the early to mid 1980s and only a small number of HIV/AIDS cases have been documented as of 1989. However, the prevalence rate of HIV/AIDS in the different regions has increased significantly in the last few years (Royce *et al*., 1997; UNAIDS, 2000).

HIV epidemics in Sub-Saharan Africa: Africa is believed to be home to at least 70% of the total adults and 80% of the total children globally living with HIV (Piwoz and Preble, 2000; UNAIDS, 2002). About 75% of all AIDS deaths have occurred in sub-Saharan Africa since the epidemic began over two decades ago. At the end of 2001, it was reported that of the 40 million people estimated to be living with HIV/AIDS, 28.5 million live in Sub-Saharan Africa. Of approximately 13.2 million children who have lost both parents due to HIV infection, 12.1 million live in Sub-Saharan Africa (UNAIDS, 2001). Available data showed that countries in southern Africa now have prevalence rates higher than 20%: Botswana (38.8%), Lesotho (31%), Namibia (22.5%), South Africa (20.1%), Swaziland (33.4%), Zambia (21.5%) and Zimbabwe (33.7%) (Maw, 2000).

Table 1: Global summary of HIV/AIDS epidemic, December 2001 (UNAIDS, 2001)

No. of people living with HIV/AIDS	Adults	37.2 million
	Men	16.9 million
	Women	17.6 million
	Children under 15 years	2.7 million
People newly infected with HIV in 2001	Adults	4.3 million
	Men	1.7 million
	Women	1.8 million
	Children under 15	8 00,000
AIDS deaths in 2001	Adults	2.4 million
	Men	720, 000
	Women	1.1 million
	Children under 15 years	580,000
AIDS in Africa	Adults and children	24.5 million

In West and Central Africa, new data confirm an increased rate. In Cameroon's urban areas, the HIV prevalence rate increased from 2% in 1988 to 4.7% in 1996. Nigeria's national prevalence rate rose from 1.9% in 1993 to 5.8% in 2001. Already about 3.5 million Nigerians are estimated to be living with HIV/AIDS (UNAIDS, 2001, 2002). The rise of HIV prevalence in conflict countries such as Angola, Burundi, the Democratic Republic of Congo and Rwanda is considered a serious concern as the extensive displacement of people and the disruption of social systems increase the vulnerability of the people to HIV infection (UNAIDS, 2001, 2002). Table 1 reveals a global summary of the HIV/AIDS epidemic.

Modes of transmission of HIV: HIV is present in peripheral blood, cell free plasma, semen, cervical and vaginal secretions, lymphnodes, brain cells, liver cells, cerebrospinal fluid (CSF) and saliva (Sabatier, 1987; DeGruchy, 1990; Soderlund *et al*.,1999; SAHIVCS, 2001). HIV can be transmitted via

- Sexual acts (horizontal transmission).
- Blood or blood products from an infected person transfused to another individual.
- Intravenous drug abuse

Needle stick injury and other parenteral modes of innoculation of the virus as well as ear piercing, tribal marks and scarifications are other methods of transmission (DeGruchy, 1990; SAHIVCS, 2001). In addition, Royce *et al*. (1997), reported that HIV can still be transmitted by people receiving Highly Active Anti-Retroviral Therapy (HAART) and/or by those who have undetectable viral loads. HIV-1 and HIV-2 are transmitted in the same ways, although there is evidence that HIV-2 is less easily transmitted through the sexual route and mother to child route than HIV-1 subtypes. Epidemiological evidence showed that HIV-1 subtypes seem to be predominant in certain epidemics (for example,

the rapid heterosexual spread of subtype E strains in Thailand). However, there is no clear evidence to link particular subtypes with a specific mode of transmission (DeVincenzi, 1994; Bartlett, 1998; Gallant, 1999).

Sexual transmission: As Royce *et al.* (1997) stated, unprotected sexual intercourse (defined as penetrative oral, vaginal or anal sex) without the use of a condom between a male and a female or between males, accounts for 75-85% of HIV infection in adults. One of the most complex factors affecting the pathogenesis of HIV infection is that of sexual transmission. Sexual transmission of HIV is dependent on a number of factors that are involved in both the person transmitting the virus and the uninfected partner (Darby *et al.*, 1996; Denny *et al.*, 1998; Oguntibeju and Fabode, 2002; Oguntibeju *et al.*, 2002). Sexual transmission of HIV may occur when a sufficient amount of the infectious virus penetrates the mucosa of an individual during sexual relations (Denny *et al.*, 1998).

It has been suggested that factors that increase the amount and virulence of the immunodeficiency virus; weaken the integrity of the localised tissue barriers, or interrupt with the production of an effective local and systemic immunological response, may increase the chances of transmission of HIV (Denny *et al.*, 1998; Cohen and Fauci, 2001). Seidlin *et al.* (1993); Weiss (1996); Royce *et al.* (1997); Denny *et al.* (1998); UNAIDS (1999); Wawer *et al.* (1999) and Maw (2000) noted that several factors are creating a fertile ground for the epidemic. These factors include host susceptibility, host genetic factors, stage of infection, rate of partner change, the biological property of HIV, mass unemployment and economic insecurity, social and cultural norms, other sexually transmitted infections and unprotected/unsafe sex.

Blood-borne transmission of HIV: Generally, blood-borne transmission of HIV occurs via needle sticks, other blood-contaminated sharp objects and via blood transfusion and organ transplantation. The people at risk are intravenous drug users, healthcare workers and recipients of blood, blood products and organs (Cardo *et al.*, 1997). Globally, by the end of 1996, blood transfusion accounted for 3-5% of all adult cases of HIV infection (Efem, 1990; Cardo *et al.*, 1997; Leroy *et al.*, 1998). Routine screening procedures have significantly reduced this risk, especially in developed countries. However, there are reported cases of HIV having been transmitted through transplantation of blood-containing or highly vascularised organs such as the kidney, liver, heart, pancreas, bone, skin and via artificial insemination (Efem, 1990; Smith and Nichols, 1991). Healthcare workers are continually at risk of acquiring blood-borne infections, in particular Hepatitis B and C viruses and HIV (Bragbjerg, 1993).

The biology of HIV: There are two types of HIV which show approximately 40-60% amino acid homology and these two types are discussed.

Type 1 (HIV-1): Type-1 is found throughout the world and is responsible for the majority of cases of HIV infection (Fox, 1996; SAHIVCS, 2001). HIV-1 strains are further divided into group M (major) and group O (outlier) strains. Group M viruses are a prevalent group accounting for most HIV-1 infections worldwide. On the other hand, the smaller group O strains are rare and are quite diverse from the group M viruses (Kuritzkes, 1999). The reason for the genetic diversity of HIV-1 is related to the inherent potential of the virus to mutate and in some instances is due to the recombination of distinct virus strains.

The initial epidemic in South Africa was due to a clade B virus, but this has been overtaken by a clade C epidemic (Martin, 2000). It was confirmed that each HIV particle is composed of two copies of the single-stranded RNA viral genome packaged inside a protein core or capsid. The core (Gag) proteins include the major structural proteins p24 (capsid) and p17 (matrix), the internal structural protein p7 (nucleocapsid) and the Gag-Pol precursor protein p55. The virus particle also contains polymerase (Pol) proteins that are essential for the early steps in the life cycle of the virus. This includes the reverse transcriptase p66/p51 and the endonuclease/integrase p31 (Pantaleo *et al.*, 1998). The capsid of HIV is surrounded by lipid envelope derived from the infected cells, in which HIV envelope glycoproteins (Env) are embedded. These comprise the outer envelope glycoprotein gp120, the transmembrane glycoprotein gp41 and the precursor glycoprotein gp160 (Vogt *et al.*, 1997; Martin, 2000).

Type 2 (HIV-2): Type 2 is currently and predominantly found in West Africa and countries with historical or commercial ties to this region (Efem, 1990; Fox, 1996). HIV-type 2 was isolated first in 1986 from AIDS patients in West Africa where it is most prevalent and mainly acquired through heterosexual relationships. The incidence of HIV-2 has also been reported from East Africa, Europe, Asia, North America and Latin America. Five HIV-2 sub-types (A-E have been described (Moore *et al.*, 1997; Young, 1997; Kuritzkes, 1999; Martin, 2000).

Cellular receptors for HIV: HIV is known to infect certain types of cells; these are cells expressing the $CD4^+$T-cell receptor. These cells include T-helper cells ($CD4^+$ T-cells or T4 cells), as well as other white blood cells, including monocytes and macrophages. Glial cells in the central nervous system, chromaffin cells in the intestine and Langerhans cells in mucous membranes and skin that express the $CD4^+$ T-cell receptor can also be infected with HIV (Bagasra *et al*., 1992; Paxon *et al*., 1996).

However, some cells, for example, neurones that do not express the $CD4^+$T-cell receptor, may become infected with HIV. This raises the possibility that other cellular targets may exist for the human immunodeficiency virus. Research findings indicate that specific human cell surface proteins identified as co-receptors in addition to the $CD4^+$T-cell, have been found to mediate fusion between HIV and its target cells (Paxon *et al*., 1996; Grossman and Herberman, 1997). Two of the prominent co-receptors are: C-C chemokine receptor CCR-5, expressed by monocytes and lymphocytes which mediate entry of Non-Syncytium Inducing (NSI), monocytotropic strains of HIV-1 and the C-X-C chemokine receptor CXCR-4 (also known as fusin)-expressed on T-lymphocytes which mediates entry of Syncytium-Inducing (SI), T-cell tropic strains of HIV-1. This possibly explains the reason why monocytotropic strains of HIV can infect both monocytes and primary (both of which express CCR-5) but not T-cell lines (which lack CCR-5 and why T-cell tropic strains of HIV-1 can not infect monocytes (which lack CXCR-4). The CCR-5 and CXCR-4 co-receptors function as receptors for chemokines in the human body system.

It has been postulated that chemokines that are produced by $CD8^+$ cells in response to immune activation, such as RANTES (regulated upon activation, normally T-cell expressed and secreted), MIP-1α and MIP 1β (macrophage inflammatory proteins), bind to CCR-5, blocking the entry of HIV-1, thereby inhibiting *in vitro* infection with monocytotropic but not T-lymphotropic strains of the virus (Cocchi *et al*., 1995; Paxon *et al*., 1996; Ullum *et al*., 1998).

Pathogenesis of HIV infection: Most characteristically, HIV-1 infection in man results in the loss of function and death of $CD4^+$T-cells with a resultant increased incidence of opportunistic infections and malignancies (Levy, 1993; Fox, 1996). Patients that are seropositive for HIV-1 positive, progress through the infection at different rates and factors that affect the progression are clues to the pathogenesis of HIV-infection (Schechter *et al*., 1994; Dalgleish and Colizzi, 1992; Levy, 1993; Kreiss *et al*., 1997). Literature tends to agree that genetic predisposition, reflected in different human leucocyte antigen (HLA) types, concurrent infections, age, dose of the inoculum, the route of exposure, the variant of the virus as well as other factors, plays a role in the pathogenesis of HIV-1 and in determining how the immune system handles the infection.

Processes of pathogenesis of HIV infection: The sequence of events associated with the processes of pathogenesis by Fox (1991), Fox *et al*. (1992), Fox and Cottler-Fox (1992), Fox *et al*. (1994) and Fox (1996) can be summarized as follows:

- HIV, covered with cell membranes, antibodies and/or complement from the infected individual enters into a new host.
- The infecting virus is immunologically recognized as an antigen complex and as such is attacked by $CD4^+$T-cells. Contact with protruding gp120 results in infection of the host cells.
- The infected cell produces many more viral particles that are not coated with antibodies and are therefore able to freely produce infection among $CD4^+$ bearing cells.
- Infected virus-producing cells shed antigens in the form of virions and viral proteins. These substances are immunogenic.
- There is lymphoid hyperplasia accompanied by B-cell expansion and increasing levels of humoral antibodies and plasma cells. This is followed by a proportionate decrease in the numbers of circulating productively infected cells. This reciprocal change in virus-producing cells may either be due to cytotoxic T-lymphocytes, or to virus inactivation by humoral antibodies or both.
- There is an accumulation of HIV as a viral-immune complex on the surface of the cell membranes of follicular dendritic cells. This is attached by Fc receptors on the cell surface. The virus reservoir is required for the progression of HIV infection and viral concentration of 1×10^9 particles per cubic centimetre may be reached in the germinal cells.
- The infected individual assumes a steady state of infection in which the $CD4^+$ T-cells become infected as they migrate through the germinal cells. It is said that depending on the time from infection to activation and viral expression, infected cells produce viral particles in the lymphoid tissue or at distant sites elsewhere in the body system.
- The depletion of $CD4^+$T-cells exceeds formation by a slight margin. This phase of the infection/disease can continue for many years.

- Due to the prolonged loss of $CD4^+$T-cells and their functional interactions, the integrity and function of the lymphoid tissues are broached and there is loss of filtration of virus/virions as well as general disorganization of the lymph nodes. Lymphoid tissues seem to depend on complex ecological interactions, modulated by cytokines and dependent on micro-environmental interaction. At some point in this process, the AIDS-defining stage is reached.
- Immune function decreases until opportunistic AIDS-defining infections overwhelm the patient.

Principles of HIV pathogenesis: Infection with HIV-1 initiates a process that leads to progressive destruction of the population of $CD4^+$T-cells with roles in the generation and maintenance of host immune responses (Fauci, 1988; Fauci *et al*., 1991; Feinberg, 1995; Koot *et al*., 1996; Haynes *et al*., 1996). The target cell preference for HIV-1 infection and depletion is determined by the identity of the $CD4^+$T-cell surface that is recognized by the HIV-1 envelope (env) glycoprotein as the virus binds to and enters host cells to initiate the virus replication cycle (Feinberg, 1995; Koot *et al*., 1996). It has been found that the process of cell fusion (syncytium formation) which depicts a significant cytopathic consequence of HIV-1 infection of $CD4^+$ T-cells, also depends on the specific interaction between $CD4^+$T-cells and the HIV-1 env glycoprotein (Feinberg, 1996; Bartlett, 1998).

Decline of $CD4^+$T-cells: After initial infection of the human host, the pace at which immunodeficiency develops and the susceptibility to opportunistic infections and malignancies become manifest and are associated with the rate of decline in $CD4^+$T-cell levels (Stein *et al*., 1992; Kaplan *et al*., 1995; Enger *et al*., 1996; USPH/IDSA, 1996). The rate of $CD4^+$T-cell decline varies considerably from person to person and is not constant throughout all stages of HIV-infection. Koot *et al.* (1996) reported that acceleration in the rate of decline of $CD4^+$ T-cell numbers heralds the progression of the disease. According to Koot *et al.* (1996), the virological and immunological processes that take place during the point of onset of a rapid fall in $CD4^+$ T-cell count are poorly understood. However, they are believed to be associated with increasing rates of HIV-1 replication *in vivo* and declining cell-mediated immune response.

Progression of HIV to AIDS: In developed countries, the average time for adults to develop AIDS after initial HIV-1infection is about 10-12 years in the absence of antiviral therapy. However, some individuals (20%) manifest full-blown AIDS within five years of infection, whereas others (<5%) have sustained long-term (>10 years) asymptomatic HIV-1 infection without significant decline in $CD4^+$T-cell counts. As Haynes *et al*. (1996) observed, about 2% of HIV-1 infected persons seem to be able to contain viral replication to extremely low levels and maintain stable $CD4^+$T-cell counts within the normal range for lengthy periods (12-15 years). Also, within this group, very rare individuals are infected with HIV-1 variants harbouring genetic defects. Most instances of slowly progressive or apparently non-progressive HIV infection are believed to result from more effective host antiviral immune responses. These individuals tend to have active reactive cytotoxic T-cell responses against HIV-1 infected cells (Haase, 1999).

Inheritance of specific gene: Inheritance of a specific gene other than the HLA gene has also been implicated in the rate of progression of HIV-1 disease. Researchers are uncertain as to whether the $CD4^+$T-cells from different individuals vary in their susceptibility to the cytopathic effect of HIV-1 infection. However, few people who are not infected with HIV-1 despite multiple exposures to the virus, display higher levels of β-chemokine production and altered expression of the specific chemokine receptors, for instance CCKR-5 that serve as co-receptors for entry to HIV-1 into target cells (Paxon *et al*., 1996; Pakker, 1998).

Age: Stein *et al*. (1992) and Darby *et al*. (1996) reported that the age of people living with HIV-1 infection could influence the rate of progression to AIDS and this suggests that the regenerative capacity of the host immune system (known to decline with age) may equally determine the integrity of the immune system (how it resists or repairs the damage caused by HIV-1 infection).

Environmental factors: Environmental factors, particularly the ones leading to activation of the immune system, may affect the rate of HIV-1 induced immunosuppression (Ho *et al*., 1995; Hu *et al*., 1996; Oguntibeju *et al*., 2002). Exposure to environmental antigens may activate HIV-1 replication, thereby increasing immune damage and enhancing progression of HIV-1 infection (Ho *et al*., 1995). The authors also believe that current HIV-1 replication in the presence of an active but incompletely effective host antiviral immune response may partly be responsible for secondary manifestations of the HIV-1 disease. Similar to the above, Kuritzkes (1999) and MacDouall (1997) argued that viral attributes such as cytopathicity, replicability, syncytiality, cell tropism, virulence and viral load, apoptosis, antigenic dominance or competition, induced or random viral escape mutants,

autoreactive cells of $CD8^+$ or $CD4^+$ phenotypes and inhibition of the production of pre-cursor cells, are sufficient to explain the pathogenesis of HIV.

Malnutrition: It has been reported that factors such as the presence of sexually transmitted diseases, tuberculosis, cultural beliefs and customs, poor economic status contribute to chronic and endemic malnutrition in Africa while malnutrition in turn affect immune function and influence viral expression and replication which further affect progression of HIV disease and mortality of the patients. Research studies have confirmed that nutrient deficiencies (resulting from malnutrition) are associated with immune dysfunction and accelerated progression to AIDS (Fawzi and Hunter, 1998; Macallan, 1999).

CONCLUSIONS

It is clear from this review that literature tends to agree that pathogenesis of HIV is not mediated by a single factor but by a combination of factors such as genetic predisposition, reflected in human different Human Leucocyte Antigen (HLA) types, concurrent infections, age, environment, dose of the inoculum, route of exposure, the variant of the virus as well as other factors. Factors which include poverty, malnutrition, religious belief but not limited to lack of commitment on part of African government combined to play a role in the spread of HIV/AIDS in Africa. Knowledge of the pathogenesis of HIV and factors contributing to spread of HIV/AIDS could provide a mechanism to develop vaccine for the treatment HIV/AIDS and combat the spread of HIV/AIDS, respectively.

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