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Review Article

Coagulation system and HIV infection: A Review

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Abstract

Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate or breast milk of the infected person to HIV free person. Within these body fluids, HIV is present as both free virus particles and virus within infected immune cells. The four major routes of transmission are unsafe sex, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth. Coagulation results from interactions among vessel wall, platelet and coagulation factors. When an injury occurs that results in bleeding, the coagulation system is activated and plugs the hole in the bleeding vessel while still keeping blood flowing through the vessels by preventing the clot from getting too large. The end result is the formation of insoluble fibrin threads that link together at the site of injury, along with aggregated cell fragments called platelets to form a stable blood clot. A number of coagulation abnormalities have been described in HIV disease including acquired deficiency states of the physiologic anticoagulants: protein C protein S and heparin cofactor II. Of these, protein S deficiencies are the most consistently observed and is present in up to 73% of HIV infected men. Most commonly there is reduction in free protein S and coordinate reduction in functional protein S activity.

Keywords: Coagulation system, HIV Infection, AIDS.

Introduction

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired Immunodeficiency Syndrome (AIDS) (Weiss, 1993). This is a condition in humans in which progressive failure of the immune system allows life threatening opportunistic infection and cancers to thrive.

Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate or breast milk of the infected person to HIV free person. Within these body fluids, HIV is present as both free virus particles and virus within infected immune cells. The four major routes of transmission are unsafe sex, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth (perinatal transmission) (Fox *et al.*, 1992).

Viruses such as HIV cannot grow or reproduce on their own, the need to infect the cells of a living organism in order to replicate. The human immune system usually detects and kills viruses fairly quickly, but HIV attacks the immune system itself, the very thing that would normally get rid of the virus. (Ascher *et al.*, 1990).

HIV is a causative organism of autoimmune deficiency syndrome which was recognized as a new disease syndrome in the early 1980's in the USA with

the unusual occurrence of pnemocystis carinii pneumonia and Kaposi's sarcoma in previously healthy young men (Greene, 1991). This retrovirus was isolated from a young homosexual man with lymphadenopathy. The virus was identified and classified in the family Retroviridae genus lentviranae (Baker *et al.,* 2007).

Under the electron microscope, the viruses were revealed as a cylindrical core with nucleic acid cloned and sequenced. The cylindrical core is 80-130nm in diameter, it has a unique three layered structure, and innermost is the genome nucleocapside complex. This complex is enclosed within a capsid which is surrounded by a host cell membrane derived envelope, from which viral envelope glycoprotein 'spikes' project. HIV infects a wide variety of tissues in humans including the marrow, lymph node, brain, skin and bowel (Baker *et al.,* 2007). This retrovirus differs from other retroviruses such as human T lymphotrophic virus (HTLV) 1 and 2. The virus was eventually named Human Immunodeficiency Virus (Cohan *et al.,* 1986).

It is transmitted mostly sexually in blood or blood products and pre-natally. The most at risk of acquiring HIV infection are homosexuals, injecting drug misusers and those with bisexual orientation. Others include individuals receiving unscreened blood or blood products, infants born of infected women.

There are various strains of HIV and are designated by a code with geographically informative letters and sequential numbers placed either in brackets, or as a number, or as a subscript. Example HIV-$_{sf33}$ and HIV - 2 (Pantaleo *et al.,* 1995)

If there is a laboratory evidence of HIV infection, certain indicator diseases that require presumptive and definitive diagnosis are diagnostic of AIDS, AIDS is an illness characterized by one or more indicator diseases (Safrit *et al.,* 1995).

Acute HIV is usually characterized by fever, malaise, lymphadenopathy and rash. These conditions are subclinical. A chronic infection of AIDS that follows is asymptomatic in early stages. If an individual is infected with this virus, the virus acts so quick destroying the immune system making the individual prone to little infections. HIV is present all over the world and the long term consequences of this pandemic will affect every country one way or another over time. This is an evolving pandemic threatening global public health and health care provision, as well as political and economic stability. (Kuby Janis, 1997).

Coagulation

This is a complex physiolosocal process by which blood forms clot. It is important part of haemostasis (the ceasation of blood loss from damaged vessel), wherein a damaged blood vessel wall is covered by a platelet and fibrin-containing clot to stop bleeding and begin repair of the damaged vessel) (Shapiro, 2003). Coagulation results from interactions among vessel wall, platelet and coagulation factors. When an injury occurs that results in bleeding, the coagulation system is activated and plugs the hole in the bleeding vessel while still keeping blood flowing through the vessels by preventing the clot from getting too large. The end result is the formation of insoluble fibrin threads that link together at the site of injury, along with aggregated cell fragments called platelets to form a stable blood clot. The clot prevents additional blood loss and remains in place until the injured areas have healed. The clot is eventually removed as the injured site is healed. In normal healthy individuals, this balance between clot formation and removal ensures that bleeding does not become excessive and that clots are removed once they are no longer needed (Shapiro, 2003).

A number of coagulation abnormalities have been described in human immunodeficiency virus (HIV) disease. High levels of plasma von Willebrand factor have been reported in HIV disease and might be indicative of activated endothelium. Endothelium is involved in important homeostatic mechanisms of non-thrombotic vascular surfaces, vascular tone regulation and immunomodulation (Karpatkin *et al.,* 2002). Injured endothelium leads to localized inflammatory response of which the direct consequence is the occurrence of occlusive thrombosis events mediated between leucocyte recruitment and platelet adhesion and aggregation, blood clothing activation and fibrinolysis derangement. HIV infection has been associated with endothelial dysfunction. Since HIV infection is associated with endothelial dysfunction it may therefore result in activation and consumption of coagulation factors and ultimately coagulation defect(Omoregie *et al.,* 2009).

In HIV infection, the liver is affected. The liver is the major organ responsible for the synthesis of most coagulation factors and infection of the liver by HIV

can lead to abnormal production of coagulation factors. The $CD4^+$ count is used to measure immune status and HIV disease progression (Tolstrup *et al.,* 2004).

Prothrombin time (PT) an activated partial thromboplastin time (APTT) are screening tests for the extrinsic and intrinsic clothing systems respectively. They detect deficiency or inhibition of clotting factors in either system, and are the first tests in screening for coagulation disorders. As HIV infection progresses, endothlieal dysfunction and liver damage will increase and this may result in severe clotting impairment.
In reference to the abnormality of coagulation in HIV positive individuals, the coagulation disorders will be investigated, by considering platelet count, prothrombin time, activated partial thromboplastin time, and blood fibrinogen concentration, as well as CD_4 count and factor VII concentration.

Platelet count is a diagnostic test that determines the number of platelets in the patient's blood. Platelet which are also called thrombocytes, are small disk-shaped blood cells produced in the bone marrow and involved in the process of blood clotting. There are normally between 150,000-450,000 platelets in each microlitre of blood. Low platelet count or abnormally shaped platelets are associated with bleeding disorders (Henry, 2001).

Prothrombin time (PT), is one of the coagulation factors produced by the liver. One of the final steps of the cascade is the conversion of Prothrombin (factor 11) to thrombin. The Prothrombin time test evaluates the integrated function of the coagulation factors that comprises the extrinsic and common pathways.

The international Normalized Ratio (INR) is used to standardize PT result gotten (Horsti *et al.,* 2005).

Activated partial thromboplastin time (APTT), is a screening test that is done to help evaluate a person's ability to form blood clot. It assesses the amount as well as the function of coagulation factors XII, IX, VII, X, V, II and I which are part of haemostasis (Pagana & Pagana, 2006).

Fibrinogen (factor 1) is a soluble plasma glycoprotein synthesized by the liver and is converted by thrombin into fibrin during blood coagulation.

Fibrinogen deficiency (hypo-fibrinogenemia) or disturbed function of fibrinogen can lead to either bleeding or thromboembolic complications (Acharga & Dimichele, 2008).

CD4 count is the number of CD4 cells per microlitre of blood. It is used to stage the patient's disease, determine the risks of opportunistic illness, assess prognosis and guide decisions about when to start antiretroviral treatment(CDC, 2009).

Human Immunodeficiency Virus (HIV)

Widespread awareness of HIV disease began with a brief report in the morbidity and weekly report, of a rare pneumonia caused by pneumocystis carinii known as pjiroveci as well as other unusual infections in five young homosexual men in Los Angeles (Ukaejiofo, 2009).

Awareness that a significant epidemic was developing grew as case reports mounted and similar immune deficiency syndromes were described in New York, California (Dovek *et al.,* 2009). And elsewhere among homosexual men, intravenous drug users, Haitians, hemophiliacs, recipients of blood transfusion, infants, female sexual partners of infected men (Masur *et al.,* 1982), prisoners and Africans (Chumeck *et al.,* 1983).
As researchers began to describe the epidemiology and risk factors and systematic way, many theories emerged regarding the cause of the mysterious disease.

In 1983 scientists at the Pasteur institute in France isolated a novel retrovirus from a young homosexual man with lymphadenopathy(Baker *et al.,* 2007). HIV infection has developed into a worldwide pandemic, with tens of millions of individuals infected by the virus and many millions more affected.

By 1985, serologic assays had been developed to test for HIV infection in asymptomatic persons, to identify new infections by seroconversion, and to screen blood donations.

In 1987, Zidovudine (AZT, or azidothymine) became the first drug approved by United State Food and Drug Administration (FDA) for the treatment of AIDs (Fischi *et al.,* 2007). Early excitement over the life extending effects of the drug soon waned, as patients treated with this single drug therapy began to experience disease progression leading to death. The epidemiology, treatment and prophylaxis of opportunistic infections associated with HIV induced immune deficiency lead to significant life saving advances.

In the mid 1990s, there was the introduction of protease inhibitors (Hammer *et al.,* 1997).

Effective combination antiretroviral therapy (ART) became the standard of care in the United States and Western Europe countries in which effective ART was available began to note declining morbidity and mortality associated with HIV infection. Patient treated with potent ART showed precipitous decreases in the amount of HIV RNA circulating in their serum, indicating interference with HIV replication. The inhibition of viral replication, CD4 T-cell counts began to increase in treated individuals, demonstrating the regenerative capacity of the damaged immune system (Ho *et al.*, 1995).

HIV infection in humans is considered pandemic by the World Health Organization (WHO). It infects vital cells in the human immune system such as helper T cell example CD4 + T cells, macrophages and dendritic cells. Like cancer, scientists continue their research in order to attempt to find a cure for this disease.

According to the website for the AIDs Research Alliance (ARA), there are currently two types of alternatives being researcher. They are prostration and Microbicides prostratin is a tropical plant used to battle illnesses such as yellow fever. The ARA believes the compound has the ability to destroy hidden and infected CD4 cells. They have performed numerous testing and is presently waiting for the permission of the food and Drug Administration for the phase I testing of actual individual with positive HIV.

Microbicides are gels or creams that can be used during sexual contact to prevent transmission.

Pathogenesis of HIV

HIV is though to have originated in non-human primates in sub Saharan Africa and was transferred to humans late in the 19th or early 20th century (Salemi, 2000) HIV had spread to at least five continents North America, South America, Europe, Africa and Australia. The first paper recognizing a pattern of opportunistic infections characteristic of AID was published in 1981. HIV is believed to have originated in West Central Africa and to have jumped species a process known as zoonosis. Zoonosis is transfer of pathogen from non human animals to humans. This requires the following conditions.

1. A human population
2. A nearby population of a host animal
3. An infectious pathogen in the host animal that can spread from animal to humans.
4. Interaction between the species to transmit enough of the pathogen to humans.
5. Ability of the pathogen to spread from human to human.
6. Process whereby the pathogen disperses widely, by either killing off its human hosts or provoking immunity.

The history of the HIV is filled with triumphs and failures. Living and death. The HIV time line began early in 1981. In July that year, the New York Times reported an outbreak of a rare form of cancer among gay men. In the beginning, the center for Disease Control (CDC) did not have an official name for the disease often referring to it by way of the diseases that were associated with it. Example lymphodenopathy, diseases after which the discoverer of HIV originally named the virus (Barre-sinouss *et al.,* 1983). This gay cancer as it was called by that time was later identified as Kaposi's sarcoma the name by which a task force had been set up in 1981. About the same time, emergency rooms in New York City began to see a rash of seemingly healthy young men presenting with fever, flu-like symptoms and a rare –pneumonia called pneumocystis.

This was the beginning of what has become the biggest health care concern in modern history.

In the general press, the term GRID which stood for gay related immune deficiency has been coined (Altman, 1982). The CDC, in search of a name and looking at the infected communities coined the 4H disease as it seemed to single out Haitians, homosexuals, hemophiliacs and heroin users.

However, after determining that AIDs was not isolated to the homosexual commonly, the term GRID became misleading and AIDs was introduced at a meeting in July 1982 (Kher, 1982). By September 1982 the CDC started using the name AIDs and properly defined the illness. The disease still plagues society taking a look back many years ago of HIV/AIDS.

1959-HIV/AIDs syndrome has been around for longer. A man residing in Africa died of a mysterious illness Decades later, after examining some blood sample taken from him, it was found to be related to an HIV infection.

1981- It was found among gay men in New York and California, also in drug addicts and people who received blood transfusion.

1983- Researchers at the Pasteur institute isolated a retrovirus which was believed to be related to the outbreak of HIV/AIDS (Baker *et al.,* 2007).

1984- A Canadian flight attendant, nicknamed partied zero dies of AIDs, because of his sexual connection to several of the first victims of HIV/AIDs.

1985 – Robert Gallo's Lab patents an HIV test kit that later is approved by the FDA, At the same time HIV/AIDs centers the public eye when Rock Hudson dies of AIDS and Ryan White is barred from his elementary school in Indiana.

1987- A treatment arrives. The drug retrovir (AZT, Zidovudon) was approved.

1990- Ryan White dies at the age of 19. That year the Ryan White care Act was enacted by congress to provide government sponsored funds for a care of HIV/AIDs infected people.

1992- Combination therapy arrives. The FDA approves the first drug to be used in combination with AZT.

1993- The British study, the Concorde trails, offers proof that AZT immunotherapy does nothing to delay progressing to AIDs IN asymptomatic patients.

History of HIV in Nigeria

The first two cases of HIV and AIDs in Nigeria were identified in 1985 and were reported at the international AIDS conference in 1986. In 1987 the Nigerian health sector established the National AIDs advisory committee, which was shortly followed by the establishment of National Expert Advisory committee on AIDs (NEACA). At first the Nigerian government was slow to respond to the increasing rates of HIV transmission and it was only in 1991 that the Federal Ministry of Health made their first attempt to assess Nigerians AIDs situation. The results showed that about 1.8 percent of the population of Nigeria was infected with HIV. During the 1990s surveillance reports revealed that HIV prevalence rose from 3.8 percent in 1993 to 4.5% in 1998.

When Obasanjo Olusegun became the president of Nigeria in 1999, HIV prevention, treatment and care became of the governments primary concerns. The president's committee on AIDs and the National Action Committee on AIDs (NACA) were created, and in 2001, the government set up a three year HIV/AIDs emergency action plan (HEAP).

In 2005 a new framework was developed covering the period from 2005 to 2009.

In 2006, it was estimated that 10 percent of HIV infected women and men were receiving treatment to reduce the risk of mother to child transmission
.
In 2010 NACA launched its comprehensive national strategic framework to cover 2010 to 2015.

The main aims of the framework are to reach 80% of sexually active adults and 80% of most at risk populations with HIV counseling and testing by 2015.

Classification of HIV

The CDC classification system for HIV infection is the medical class system used by the United States Centres for Disease Control and prevention to classify HIV disease and infection.

HIV is a highly variable virus which mutates very readily. This means there are many different strains of HIV, even within the body of a single infected person Bases on genetic similarities, the numerous virus strains may be classified into types, groups and sub types.

There are two types of HIV. HIV -1 and HIV -2. It seems that HIV-2 is less easily transmitted and the period between initial infection and illness is longer. Worldwide, the predominant virus is HIV-1

The relatively uncommon HIV -2 type is concentrated in West Africa and its rarely found elsewhere. These lentiviruses have many morphologies and biological properties in common. Many species affected with lentivirus have long duration illnesses with a long incubation time (Levy, 1993). Lentiviruses are transmitted as single stranded, positive sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted into double stranded DNA by a virally encoded reverse transcriptase that is transmitted along with the viral genome in the virus particle. The viral DNA is imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors (Smith *et al.,* 2006).

Once integrated, the virus become latent, allowing the virus and its host cell to avoid detection by the immune system.

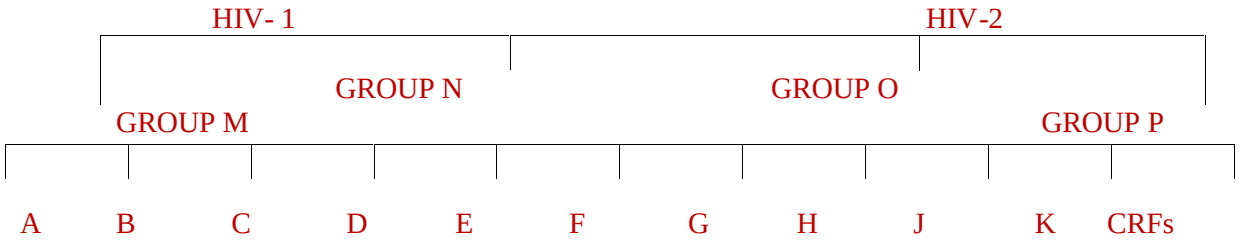

Figure 1. The different levels of HIV classification.

Human Immunodeficiency Virus -1 (HIV-1)

It was initially discovered and termed both LAV and HTLV-II. It is more virulent, more infective (Gilbert *et al.*, 2003). It is the cause of the majority of HIV infections globally. It appears to have originated in Southern Cameroon through the evolution of SIV (CPZ), a Simian Immunodeficiency Virus (SIV) that infects wild chimpanzees (Marx *et al.*, 2001).

HIV-1 viruses may be further divided into groups - Major and minor. Group M (major) and two or more minor groups. The group M viruses predominate and are responsible for the AIDs pandemic. It is the most common type of HIV with more that 90% of HIV/AIDs cases deriving form infection with HIV group M. The M group is subdivided into subtypes that are also circulating recombination forms. The subtypes are A,B,C,D,E,F,G,H,J,K,.

Subtypes A-Common in West Africa (Bobkov *et al.*, 2004).
Subtype B- it is the dominant form in Europe, the Americans, Japan, Thailand and Australia (Goudmit, 1997)
Subtype C: - It is the dominant form in Southern Africa, India and Nepal (Goudmit, 1997).
Subtype D: - is only seen in Eastern and central Africa.
Subtype E: - It has never been identified as a non recombinant, only recombinant with subtype A as CRFO1-AE.
Subtype F: - It has been found in central Africa, South America and Eastern Europe.
Subtype G: - This type and the CRPO2-AG have been found in Africa and Central Europe.
Subtype H: - It is limited in Central Africa.
Subtype J: - It is primarily found in North, central and West Africa and the Caribbean (Hemelaar *et al.*, 2006).
Subtype K: - It is limited to the Democratic Republic of Congo and Cameroon.
These subtypes are sometimes split into sub-sub types such as A1 and A2 or F1 and F2.

The other groups are the minor groups. Group N, O, and P. Group N stands for non-M, non –O. It was discovered in 1998 and has been seen in Cameroon. Only ten group N infections had been identified as of 2006 (Julie *et al.*, 2006).
Group O (outlier) group is not usually seen outside of West Central Africa. It is reportedly most common in Cameroon, about 2% of HIV positive samples were from group O (Peeters *et al.*, 1997). The group cannot be detected by early versions of the HIV-1 test kits. More advanced HIV tests have been developed to detect both group O and group N.

Group P in 2009 a newly analyzed HIV sequence was reported to have great similarity to a simian immunodeficiency virus recently discovered in wild gorillas. (Sivgor) than to SIVS from Chimpanzees (SIVCPZ). The virus had been isolated from a Cameroonian woman residing in France who was diagnosed with HIV-1 infection in 2004. The scientists placed it in a proposed group P pending the identification of further human cases (Plantier *et al.*, 2009).

Human Immunodeficiency Virus-2 (HIV-2)

It has been widely seen outside of Africa. The first case in the United States was in 1987. As of 2010 there are 8 known HIV-2 groups A to H) of these groups A and B are epidemic. Groups A spread mainly in West Africa, but also in Brazil and limitedly in Europe while group B is mainly confined to West Africa (Marx *et al.*, 2001).

HIV-2 mostly related to simian immunodeficiency virus endemic in sooty mangabers (Cercocebus aty atys) (SIVSMM), a monkey species inhabiting the forest of titorial West Africa. The groups of HIV-2 A and B spread considerably in humans.

There are six addition known HIV-2 group, each having been found in at lest one person. Groups C and D have been found in two people from Liberia, groups E and F in two people from sierra Leone, groups G and H in two people from Ivory Coast. These two strains of HIV are dead end infections, and each of them is mostly closely related to SIVSMM strains from sooty mangabers living in the same country where the human infection was found (Santiago *et al.*, 2005)

Similarities are as follows:

1. The mode of transmission is the same through exposure to bodily fluids such as blood, semen, tears and virginal fluids.
2. Both can develop into AIDS.

The differences are shown in the table below.

Table 2.1: The differences between the two strains of HIV.

Specie	HIV -1	HIV-2
Virulence	High	Low
Infectivity	High	Low
Prevalence	Global	West Africa
Inferred origin	Common Chimpanzee	Sooty Mangabey

Epidemiology of HIV

Over the past 25years, the global number of the people estimated to have HIV infection has risen every year. Some encouraging changes are being seen in the epidemiological direction of this pandemic. From its discovery in 1981 to 2006, AIDs killed more than 25 million lives down from a global peak of 2.1 million in 2004. Approximately 260,000 children died of AIDS in 2009. A disproportionate number of AIDs deaths occur in sub Saharan African retarding economic growth and exacerbating the burden of poverty (Greener, 2002). In 2005, it was estimated that HIV would infect 90 million people in Africa, resulting in a minimum estimate of 18 million orphans. In 2007 estimated 33.2 million people in the world were living with HIV, Every day during 2007 more than 6,800 people became infected with HIV, 5% of them under the age of 25. The percentage of the global prevalence has stabilized since 2000; the actual number living with the infection is increasing each year. This is because of the accumulation of new infections in people with longer survival times in a continuously growing general world population. This has resulted in the annual global increase in the estimate number of people living with HIV. Antiretroviral therapy programs since 2004 has helped to turn the tide of AIDs deaths and new infections in many parts of the world.

Disease progression

HIV disease is a continuum of progressive damage to the immune system from the time of infection to the manifestation of severe immunologic damage by opportunistic infections that define AIDs. The time it takes to transverse this spectrum varies greatly.

The period from infection to development of AIDs is incubation period. The period from an AIDs diagnosis to death is AIDs survival time. The epidemiology of HIV disease progression has attempted to characterize the distribution of possible lengths of the incubation period in the AIDs survival time, to identify laboratory tests useful for prognosis and treatment decisions and to determine what co factors accelerate or retard the rate of disease progression. Factors such as host susceptibility genetic and immune function (Morgan, 2002), as well as viral genetic variability (Campbell, 2004), may affect the rate of progression to AIDs.

- **Rapid progressors**: A small percentage of HIV infected individual rapidly progress to AIDs within four years after primary HIV (Anzala et al, 1995).
- **Long term non progressors**: Another subset of individuals who are persistently infected with HIV-1, but show no signs of disease progression for over 12 year and remain asymptomatic. Long term non progressors.

- (LTNP) are a monomer as that progression towards AIDs and occur even after 15 years of stable infection (Harrer, 1996). Some LTNP are infected with HIV that replicates inefficiently, and others are infected with HIV that is virally fit and replicates normally. The infected individual has had a strong and broad set of HIV-specific humoral and cell mediated responses.
- **Long term survivors (LTS)**: Individuals who experience signs of progression, but whose clinical and laboratory parameters remain stable over long period of time. The HIV-1 subtype that an individual becomes infected with can be a major factor in the type of progression from sero-conversion to AIDS.

Modes of Transmission

The HIV virus is passed from one person to another through blood to blood, and sexual contact. An infected pregnant woman can pass HIV to her baby. HIV can be transmitted through body fluids such as blood and any body fluid containing blood, semen, breast milk, vaginal fluid, and amniotic fluid. It is also present in saliva and sweet, but in low quantities.

The transmission through different routes is possible.

- **Sexual Exposure**: Sexual transmission occurs with the contact between sexual secretions of one person with the rectal, genital or oral mucous membranes of another. This is the more mode of transmission, as protection is rarely employed and physical trauma to vagina frequently occurs facilitating transmission (Ukaejiofo, 2009). Other sexually transmitted infections increase the risk of HIV transmission and infection, because the cause the disruption of the normal epithelial barrier by genital ulceration. Transmission of HIV depends on the infectiousness of the index case and the susceptibility of uninfected partner. In high income countries, the risk of female to male transmission is 0.04% per act and male to female is 0.08%. These rates are 4-10 times higher in low income countries (Bioly *et al.,* 2009). To reduce HIV transmission through sexual exposure programmes that aim to encourage sexual abstinence while also encouraging and teaching safer sex strategies for the sexually active can be introduced.

- **Blood products**: If infected blood comes into contact with any one wound, HIV may be transmitted. This transmission route can account for infections in intravenous drug users and recipients of blood transfusion. Sharing and reusing syringes contaminated with HIV infected blood, receiving tattoos and piercing can also be at risk of infection. WHO estimates that approximately 2.5% of all HIV infections in sub- Saharan Africa are transmitted through unsafe healthcare injections (Ukaejiofo, 2009).

- **Parental Transmission**: This transmission type can occur in utero during pregnancy, intrapartum or via breast feeding. In the absence of treatment, the transmission rate up to birth between the mother and child is around 25%. Breast feeding increases the risk of transmission by about 4%. This can be completely prevented by avoidance of breast feeding. Exclusive breast feeding and the provision of extended anti-retroviral prophylaxis to the infant are also officious in avoiding transmission.

Stages of hiv infection

HIV infects cells in the immune system and the central nervous system. One of the main type of cells that HIV infects is the T helper lymphocyte. These cells play a crucial role in the immune system. A large reduction in the number of T helper cells weakens the immune system. It infects the T helper cell because it has the protein CD4 on its surface which HIV uses to attach itself to the cell before gaining entry. Over time, the infection leads to a severe reduction in the number of T helper cells available to help fight disease.

HIV infection can be broken down into four distinct stages.

- Primary infection
- Clinically asymptomatic stage
- Symptomatic HIV infection
- Progression from HIV to AIDs

Table 2:2 WHO Clinical staging of HIV in adults and adolescent.

STAGE I	STAGE 2	STAGE 3	STAGE 4
Asymptomatic	Moderate unexpected weight loss	Unexpected severe weight loss	HIV wasting syndrome
Persistent generalized lymphadenopathy	Recurrent respiratory tract infection	Persistent oral candidisis	Pneumocystic pneumonia
	Herpes Zoster	Pulmonary tuberculosis	Karposi sarcoma
	Angular Cheilitis		Extra pulmonary tuberculosis
	Fungal nail infection		

Primary HIV infection

This stage lasts for a few weeks and its often accompanied by a short flu-like illness. In up to about 20% of people the HIV symptoms are serious but the diagnosis is frequently missed.

During this stage there is a large amount of HIV in the peripheral blood and the immune system begins to respond to the virus by producing HIV antibodies and cytotoxic lymphocytes. This process is known as seroconversion.

Clinically asymptomatic stage

This stage lasts for an average of 10 years and its free from major symptoms. The level of HIV in the peripheral blood drops to very low level but people remain infections and HIV antibodies are detectable in the blood. HIV is not dormant during this stage, but is very active in the lymph nodes.

Symptomatic HIV infection

Over time the immune system becomes severely damaged by HIV. This is thought to happen for three man reasons by HIV.

1. The lymph nodes and tissues become damaged because of years of activity.
2. HIV mutates and becomes more pathogenic, stronger and more varied, leading to more T helper cell destruction.
3. The body fails to keep up with replacing the T helper cells that are lost.
4. In this stage, infections can occur in almost all body systems. This is mainly caused by the emergence of certain opportunistic infections that the immune system would normally prevent.

Progression of HIV to AIDs

As the immune system becomes more and more damaged the individual may develop increasingly severe opportunistic infections and cancers, leading to an AIDs diagnosis. A clinical criteria is used by WHO to diagnose the progression to AIDs, this differs slightly between adults and children. In adults and children (aged 5 and over) the progression is diagnosed and the CD4 count is less than 200 cells/mm3 or a CD4 percentage less than 1.5. the WHO has developed a staging system for HIV disease based on clinical symptoms, which may be used to guide medical decision making. This was done because in resource poor communities, medical facilities are sometimes poorly equipped and viral load test results to determine the right time to begin antiretroviral treatment is not possible.

Structure of HIV

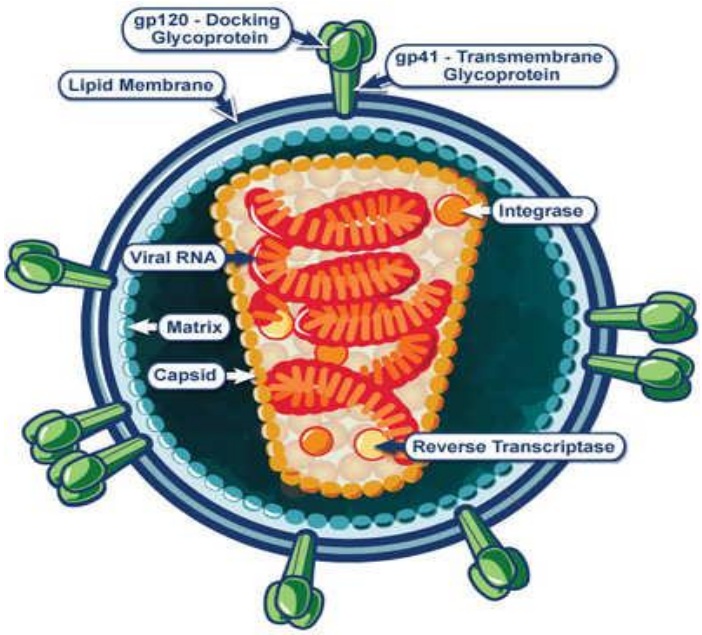

Figure 2: Structure of HIV (Ratner *et al.*, 1985)

HIV is different in structure from other retroviruses. It is around 120nm in diameter (around 60 times smaller than the red blood cell) and roughly spherical. The surface of each particle is studded with lots of little spikes. HIV particle surround themselves with a coat of fatty material known as the viral envelope. Projecting from this are around 72 spikes formed from the proteins gp 120 and gp 41. Just below the viral envelope is a layer called the matrix, which is made

from the protein p17. The protein gp 120 and gp 41 make up the spikes that project from HIV particles, while p17 forms the matrix and p24 forms the core. Inside the core are three enzymes for HIV replication called reverse transcriptase, integrase and protease. Also held within the core is HIV's genetic material, which consists of two identical strands of RNA.

The RNA component is 9749 nucleotides long (Ratner *et al.,* 1985). This is in turn surrounded by a plasma membrane of host-cell origin. The single strand RNA is tightly bound to the nucleocapsid proteins, pp6, p7 and enzymes that are indispensable for development of the viron, such as reverse transcriptase and integrase. The p6 and p7 associate with the genomic RNA and protect RNA from digestion by nucleases. A matrix composed of an association of the viral protein p 17 surrounds the capsid, ensuring the integrity of the viron particle.The envelop is formed when the capsid buds from the host cell, taking some of the host cell membrane with it. The envelope includes the glycoprotein gp120 and gp41. The structure of the virus envelope spike is of importance because of its role in virus cell attachment. It is hoped that determing the envelope spike's structure would contribute to scientific understanding of the virus and its replication cycle, and help in the creation of a cure (Zhu *et al.,* 2006).

Sign and symptoms

Symptoms related to HIV are usually due to an infection in part of the body.

Early signs and Symptoms

Some people experience signs and symptoms of HIV as soon as they become infected, while others do not. Early signs and symptoms are often mistaken for mild viral infection. Initial signs and symptoms include Headache, fever, Tiredness, Nausea, Diarrhea. It can be a life threatening problem if not treated correctly and rapidly, Enlarged lymph nodes in the neck, armpits or grin. These signs are similar to manydifferent viral infections. The only way to know if it's HIV is to get tested.

Later signs and symptoms

The center for Disease Control (CDC) says the following signs and symptoms may be warning signs of late stage HIV infection.

Rapid weight loss, dry cough, recurring fever or protase night sweats, swollen lymph glands in the armpits, diarrhea lasting more than a week, white spots or unusual blemishes on the tongue, in the mouth or in the throat, pneumonia, red, brown, pink or purplish blotches on or under the skin, depression and other neurological disorders.

HIV destroys the white blood cells that are required to fight infection.

Prognosis of HIV Infection

The prognosis of HIV infected individuals is quite variable in most adults, the average time between the entry of the virus into the body and development of AIDs is 10-11 years (Hogg *et al.,* 2001). However, in certain individuals (about 20%) AIDS is manifested within 65 years of infection yet another 12% of individuals remain free of AIDs for years (Korber *et al.,* 2000). A parameter used for prognostication is the amount of HIV-1 RNA in the plasma soon after seroconversion. Shortly after entry into the body, there is a burst viremia. The subsequent immune response results in a steady-state level of the viral particles in the plasma. This number which is variable in various individual serves as the predictor of long term outcome of the disease.

As treatments continue to be developed and because HIV continues to evolve resistance to treatments, estimates of survival time are likely to continue to change. Without antiretroviral therapy, death normally occurs within a year after the individual progresses to AIDs (Morgan *et al.*, 2002).

Diagnosis and treatment

Many HIV negative people are unaware that they are infected with the virus. For example less than1% of the sexually active urban population in Africa have been tested and this proportion is even lower in rural populations (Kumaranyake & Walts, 2001).

Only 0.5% of pregnant women attending urban health facilities are counseled, tested or receive their test results.

Again this proportion is lower in rural health facilities since donors may be unaware of their infection. HIV-1 testing consists of initial screening with an genome linked immunosorbent assay (ELISA) to detect anti-bodies to HIV-1. Specimens with a non-reactive to a

non result from the initial ELISA are considered HIV negative unless new exposure to an infected partner. Specimens with a reactive ELISA result are retested in duplicate. If the result of either duplicate test is reactive, the specimen is reported as repeatedly reactive and undergoes confirmatory testing with a more specific supplementary test.

Example:

Western blot or an immunofluorescence assay (IFA). Only specimens that are repeatedly reactive by ELISA are positive by IFA or reactive by Western blot are considered HIV positive and indicative of HIV infection. Specimens that are repeatedly reactive by ELISA are positive and indicative of HIV infection. Specimens that are repeatedly ELISA reactive occasionally provide an indeterminate western blot result, which may be either an incomplete antibody response to HIV in an infected person (Celum *et al.*, 1991).

A second specimen should be collected more than a month to later and retested for persons with indeterminate western blot results.

Nucleic acid testing e.g. viral RNA or proviral DNA amplification method can also help diagnosis in certain situations.

Treatment

Doctors often recommend drug therapy for patients who are committed to taking all their medications and have CD4 count below 500 cells/mm^3 indicating their immune system is suppressed. Some people, like pregnant women may need treatment regardless of their CD4 count. These drugs have become available over the past several years to fight both the HIV infections and cancers. They are called highly active antiretroviral therapy (HAART) and have substantially reduced HIV-related complications and deaths. There is no cure for HIV/AIDS.

Current HAART options are combinations consisting of at least three drugs belonging to at least two types of antiretroviral agents. The types are 2 nucleoside analogue reverse transcriptase inhibitor (NARTIS) plus either a protease inhibitor. Hart neither cures the patient nor uniformly remove all symptoms. This has lead to a large reduction in HIV associated morbidity and mortality in the developed countries of the world. (Palella *et al.*, 1998).

Coagulation

Coagulation is a complex physiologic process by which blood forms clots. It is an important part of heamostasis (the cessation of blood loss from a damaged vessel), wherein a damaged blood vessel wall is covered by a platelet and fibrin-containing clot to stop bleeding and begin repair of the damaged vessel (Shapiro, 2003). Disorders of coagulation can lead to an increased risk of bleeding (hemorrhage) or obstructive clotting (thrombosis)

Coagulation involves both a cellular (platelet) and a protein (coagulation factor) component. The system in humans has been the most extensively researched and is therefore the best understood (Norris, 2003).

Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium (lining of the vessel) (Cotran *et al.*, 2005) Exposure of the blood to proteins such as tissue factor initiates changes to blood platelets and the plasma protein fibrinogen, a clotting factors, platelets immediately form a plug at the site of injury, this is called primary heamostasis. The secondary haemotasis occurs simultaneously: proteins in the blood plasma, called coagulatum factors respond in a complex cascade to form fibrin strands, which strengthen the platelet plug (Furie & Furie, 2005).

Initial discoveries

Theories on the coagulation of blood have existed since antiquity. A physiologist Johannes Muller (1801-1858) described fibrin, the substance of a thrombus. Its soluble precursor, fibrinogen, was thus named by Rudolf Virchow (1821-1902), and isolated chemically by Prosper Sylvain Denis (1799-1863). Alexander Schmidt suggested that the conversion from fibrinogen to fibrin is the result of an enzymatic process, and labeled the hypothetical enzyme “thrombin” and its precursor “Prothrombin”. Arthur discovered in 1890 that calcium was essential in coagulation. (Giangrande, 2003: Shapiro, 2003).

The theory that thrombin is generated by the presence of tissue factor was consolidated by Paul Morawitz in 1905. At this stage, it was known that thrombokinase/thromboplastin (factor III) is released by damaged tissues, reacting with Prothrombin (II), which, together with calcium (IV), forms thrombin, which converts fibrinogen into fibrin (1) (Giangrande, 2003).

Coagulation factors discoveries

The remainder of the biochemical factors in the process of coagulation was largely discovered in the 20th century.

A first clue to the actual complexity of the system of coagulation was the discovery of porcelaerin (initially and later called factor V) by Paul Owren (1905-1990) in 1947. He also postulated its function to be the generation of accelerin (Factor Vi), which later turned out to be the activated form of V (or Va); hence, VI is not now in active use.

Factor VII (also known as serum Prothrombin conversion accelerator or proconvertin, precipitated by barium sulfate) was discovered in a young female patient in 1949 and 1951 by different groups.

Factor VIII turned out to be deficient in the clinically recognized but etiologically elusive haemophilia A; It was identified in the 1950's and is alternatively called antihemophilic globulin due to its capability to correct heamophilia A.

Factor IX was discovered in 1952 in a young patient with hemophilia B named Stephen Christmas (1947-1993). His deficiency was described by Dr. Rosemary Biggs and professor. R.G. MacFarlane in Oxford, UK. The factor is hence, called Christmas factor. Christmas lived in Canada, and campaigned for blood transfusion safety until he succumbed to transfusion-related AIDS at age 46. An alternative name for the factor is plasma thromboplastin component, given by an independent group in California.

Hagemen factor, now known as factor XII, was identified in 1955 in an asymptomatic patient with a prolonged bleeding time named John Hageman. Factor X, or Stuart Power factor, followed, in 1956. This protein was identified in a Miss. Audrey Prowers of London, who had a lifelong bleeding tendency. In 1957, an American group identified the same factor in a Mr. Rufus Stuart. Factors XI and XIII were identified in 1953 and 1961, respectively.

The view that the coagulation process is a "cascade" or "waterfall" was enunciated almost simultaneously by Macfarlane in 1964 in the UK and by Davie and Ratnoff in the USA, respectively (Giangrande, 2003).

Coagulation factors

Coagulation factors are a group of proteins essentials for blood clot formation. When a patient has an unexplained bleeding episode, one possible cause is a reduction in the level of a coagulation factor in their blood (Shapiro, 2003). Measuring the level of these factors can help doctors determine the cause of the bleeding and the best treatment. Levels may also be measured if someone has a family history of bleeding. In most cases, the level of a coagulation factor is determined by measuring the activity or function of the factor in blood. Activity assays can detect reduced level of a protein or proteins that don't work properly (have reduced function). Rarely, the antigen level o a coagulation factors may be measured. Coagulation factor antigen test can tell how much of the protein is present but not whether its function is normal (Takatoshi *et al.*, 1994)

When an injury occurs that results in bleeding, the coagulation system is activated and plugs the hole in the bleeding vessels with a clot while still keeping blood flowing through the vessel by preventing the clot from getting too large. The coagulation system consists of proteins (coagulation factors) that activate in step-by-step process called the coagulation cascade. The end result is the formation of insoluble fibrin threads that links together at the site of injury, along with aggregate cell fragments called platelets to form a stable blood clot (Shapiro, 2003).

Nomenclature

The usage of Roman numerals rather than eponyms or systematic names was agreed upon during annual conferences (starting in 1955) of heamostasis experts. In 1962, consensus was achieved on the numbering of factors 1-XII (Wright, 1962). This committee evolved into the present-day international committee on thrombosis and heamostasis (ICTH). Assignment of numerals ceased in 1963 after the naming of Factor XIII. The names Fletcher Factor and Fitzgerald Factor were given to further coagulation-related proteins, namely prekallikrein and high-moleculaar-weighst kininogen, respectively.

Factors III and VI are unassigned, as thromboplastin was never identified, and actually turned out to consist f ten further factors, and accelerin was found to be activated factor V. (Giangrande, 2003).

The coagulation cascade of secondary Heamostasis

The coagulation cascade of secondary heamostasis has two pathways which lead to fibrin formation. These are the contact activation pathway (also known as the intrinsic pathway), and the tissue factor pathway (also

known as the extrinsic pathway). It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway (Kamath *et al.,* 2001).

It is now known that the primary pathway for the initiation of blood coagulation is the tissue factor pathway. The pathways are a series of reactions, in which a zymogen (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are activated to become active components that then catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin. Coagulation actors are generally indicated by Roman numerals, with a lowercase appended to indicate an active form.

The coagulation factors are generally serine proteases (enzymes). There are some exceptions. For example, FVIII and FV are glycoproteins, and Factor XIII is a transglutaminase. Serine proteases act by cleaving other proteins at specific sites. The coagulation factors circulate as inactive zymogens. The coagulation cascade is classically divided into three pathways (Furie & Furie, 2005). The tissue factor and contact activation pathways both activate the "common pathway" of factor X, thrombin and fibrin.

Tissue factor pathway (Extrinsic)

The main role of the tissue factor pathway is to generate a "thrombin burst", a process by which thrombin, the most important constituent of the coagulation cascade in term of its feedback activation roles, is released instantaneously. FVIIa circulates in a higher amount than any other activated coagulation factor (Gilbert & Arenna, 1997).

Following damage to the blood vessel, FVII leaves the circulation and comes into contact with tissue factor (TF) expressed on tissue-factor-bearing cells (stromal fibroblasts and leukocytes), forming an activated complex (TF-FVIIa), TF-FVIIa activates FIX and FX.

FVII is itself activated by thrombin, FXIa, FXII and FXa. The activation of FX (to form FXa) by TF-FVIIa is almost immediately inhibited by tissue factor pathway inhibitor (TFPI) FXa and its co-factor FVa from the prothrombinase complex, which activates Prothrombin to thrombin.

Thrombin then activates other components of the coagulation cascade, including FV and FVIII (which activates FXI, which, in turns, activates FIX), and activates and releases FVIII from being bound to vWF. FVIIIa is the co-factor of FIXa, and together they form the "tenase" complex, which activates FX, and so the cycle continues. ("Tenase" is a contraction of "ten" and the suffic –"ase" used for enzymes) (Gilbert & Arenna, 1997).

Contact activation pathway (Intrinsic)

The contact activation pathway begins with formation of the primary complex on collagen by high – molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that patients with severe deficiencies of FXII, HMWK, and prekallikrein do not have a bleeding disorder (Kamath et al, 2001). Instead, contact activation system seems to be more involved in inflammation. Patients without FXII (Hageman factor) suffer from constant infection.

The common pathway

Thrombin has a large array of functions. Its primary role is the conversion of fibrinogen to fibrin, the building block of a haemostatic plug. In addition, it activates factors VIII and V and their inhibitor protein C (in the presence of thrombomodulin), and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers (Kamath *et al.,* 2001)

Following activation by the contact factor or tissue factor pathways, the coagulation cascade is maintained in a prothrerombotic state by the continued activation of FVIII and FIX to form the tenase complex, until it is down-regulated by the anticoagulant pathways.

Cofactors

Various substances are required for the proper functioning of the coagulation cascade:

Calcium and phospholipids (a platelet membrane constituent) are required for the tenase and prothrombinase complexes to function. Calcium mediates the binding of the complexes via the terminal gamma-carboxy residues on FXa and FIXa to the phospholipids surfaces expressed by platelets, as well as procoagulant micro particles or micro vesicles shed

from them. Calcium is also required at other points in the coagulation cascade.

Vitamin K is an essential factor to a hepatic gamma – glutamyl carboxylase that adds a carboxyl group to glutamic acid residues on factors II, VII, IX and X, as well as Protein S, Protein C and Protein Z (Esmon, 2003). In adding the gamma –carboxyl group to glutamate residues on the immature clotting factors, Vitamin K is itself oxidized. Another enzyme, Vitamin K epoxide reeducates, (VKORC) reduces Vitamin K back to its active form. Vitamin K Epoxide reeducates is pharmacologically important as a target for anticoagulant drugs warfarin and related coumarins such as acenocosumarol, phenoprocosumon, and dicumarol. These drugs create a deficiency of reduced vitamin K by blocking VKORC, thereby inhibiting maturation of clotting factors (Oldenburg *et al.*, 2006). Other deficiencies of Vitamin K (e.g. in malabsorption), or disease (hepatocellular carcinoma) impairs the function of the enzyme and leads to the formation of PAIVKAs (proteins formed in vitamin K absence); this causes partial or non-gamma carboxylation, and affects the coagulations factors' ability to bind to expressed phospholipids (Oldenburg *et al.*, 2006).

Regulators

Five mechanisms keep platelet activation and the coagulation cascade in check. Abnormalities can lead to an increased tendency toward thrombosis.

Protein C is a major physiological anticoagulant. It is a vitamin K-dependent serine protease enzyme that is activated by thrombin into activated protein C (APC). Protein C is activated in a sequence that starts with Protein C and thrombin binding to a cell surface protein thrombomodulin (Esmon, 2003). Thrombomodulin binds these proteins in such a way that it activates Protein C. The activated form along with protein S and a phospholipid as cofactors, degrades FVa and FVIIIa. Quantitative or qualitative deficiency of either may lead to thrombophilia (a tendency to develop thrombosis). Impaired action of protein C (activated Protein C resistance), for example by having the "Leiden" variant of Factor V or high levels of FVIII also may lead to a thrombotic tendency.

Antithrombvin is a serine protease inhibitor (serpin) that degrades the serine proteases: thrombin, FIXa, FXa, FXIa, and FXIIa., it is constantly active, but its adhesion to these factors is increased by the presence of heparin sulfate (a glycoaminoglycan) or the administration of heparins (different heparinoids increase affinity to FXa, thrombin, or both). Quantitative or qualitative deficiency of antithrombin (inborn or acquired, e.g, in proteinuria) leads to thrombophilia.

Tissue factor pathway inhibitor (TFPI) limits the action of tissue factor (TF). It also inhibits excessive TF-mediated activation of FIX and FX (Warn-Cramer *et al.*, 1998).

Plasmin is generated by proteolytic cleavage of plasminogen, a plasma protein synthesized in the liver. This cleavage is catalyzed by tissue plasminogen activator (t-PA), which is synthesized and secreted by endothelium. Plasmin proteolytically cleaves fibrin into fibrin degradation products that inhibit excessive fibrin formation. Prostacyclin (PGI2) is released by endothelium and activates platelet Gs protein-linked receptors (Hajjar, 1995). This, in turn activates adenyl cyclase, which synthesies cAMP. cAMP inhibits platelet activation by decreasing cytosolic levels of calcium and, by doing so, inhibits the releases of granules that would lead to activation of additional platelets and the coagulation cascade.

Haemostasis

Heamostasis is a process that prevents excessive blood loss in the body. It consists of a 3 –step procedure (Tortora & Grabowski, 1996).

- Primary Haemostasis. Vascular spasm and platelet plug formation
- Secondary Heamostasis or blood clotting of the plasma.
- Fibrinolysis

Platelet plug formation

Platelet plug formation is a more complex process than vascular spasm, and it occurs in three phases.
Platelet adhesion- the first phase begins when platelets detect damage to a blood vessel and begin to adhere to the exposed surfaces (Holmsen, 1994)

Platelet releases reaction- Once stuck to a site of damage, the platelets begin to change. Firstly they create extensions so that they can contact each other, and then they release their contents. There are two types of chemical packages (granules) held within the cytoplasm of platelets: alpha granules that contain clotting factors, growth factors, and fibroblasts: and

dense granules that contain ADP, ATP, calcium ions, and serotonin. Other components are also present within the platelet that aids its work. Nearby platelets are stimulated into action by the release of ADP and Thromboxane A2 (a prostaglandin found within platelets). Thromboxane and serotonin act to cause vasoconstriction (Holmsen, 1994).

Platelet aggregation-The ADP acts to make the nearby platelets sticky and adhere to the other recruited platelets, and when the collection is large enough it creates a platelet plug stopping the loss of blood through holes in small vessels.

Fibrinolysis

Fibrinolysis is the process of dissolving a clot, buy removing the fibrin within it. Plasminogen is activated by factors circulating in the blood and present in endothelial tissue (Tortora & Grabowski, 1996). In its active form it becomes plasmin or fibrinolysin which is capable of digesting fibrin fibers and inactivating certain clotting factors.

Despite these mechanisms, homeostatic imbalances can occur and clots can form atherosclerotic plaque, trauma, or infection can roughen the insides of blood vessels and attract the adhesion of platelets. Clotting in an unbroken vessel is called thrombosis and the clot itself is called a thrombus. If the clot breaks free and is transported, it is called an embolus. The embolus can become lodged in a vital organ such as the lungs or vessels surviving the brain and death may result.

Plasmin is produced in an inactive form, plasminogen, in the liver. Although plasminogen cannot cleave fibrin, it still has an affinity for it, and is incorporated into the clots when it is formed (Tortora & Grabowski, 1996).

The liver and coagulation

The liver is a vital organ present in vertebrates and some other animals. It has a wide range of functions, including protein synthesis, and production of biochemical's necessary for digestion, metabolism, glycogen storage, and decomposition of red blood cells, hormone production, and detoxification.

The liver plays a major role in heamostasis, as most of the coagulation factors, anticoagulant proteins and components of the fibrinolysis system are synthesized by hepatic parenchymal cells. Additionally, the reticuloendothelial system of the liver helps to regulate coagulation and fibrinolysis by clearing these coagulation factors from the circulation. Finally, because the liver is a highly vascularized organ with vital venous systems draining through the parenchyma, liver diseases can affect abdominal blood flow and predispose patients to significant bleeding problems (Cesarman-Maus & Hajjar, 2005).

The liver is the primary site of synthesis of most of the clotting factors and the proteins involved in the fibrinolysis system. These include all the vitamin K-dependent coagulation proteins (factors II, VII, IX, X, protein C, protein S a protein z), as well as factor V, XIII, fibrinogen, antithrombin, %2 –PI and plasminogen.

The notable exceptions are von Willebrand factor (VWF), tPA, thrombomodulin, TPFI and uPA. The VWF, tPA, thrombomodulin, TPFI are synthesized in endothelial cells, while uPA is expressed by endothelial cells, macrophages, renal epithelial cells and some tumor cells. (Cesarman-Maus & Hajjar, 2005).

Vitamin K, a fat-soluble vitamin, is required to achieve proper levels of procoagulant factors (III, VIII, IX and X) and anticoagulant factors (proteins C, S and Z). These factors require vitamin K as a cofactor for post-ribosomal modification to render them physiologically active.

Also the liver plays a vital role in the regulation of anticoagulation. Removal of activated clotting and fibrinolysis factors, especially tPA, is mediated through the hepatic reticuloendothelial system (Greenberg & Davie, 2001).

Platelet

Platelets are nonnucleated cells derived from megakaryocytes in the bone marrow and normally live in the peripheral circulation for as long as 10 days and 1.5 -3.5 in diameter, but may be lager in some disease state and a mean cell volume of around 5-6 fl. Platelets are derived from the megakaryocytes in the bone marrow. These megakaryocytes arise by a process of differentiation from the haemopoietic stem cell and Cundergo fragmentation of their cytoplasm to produce platelets. Platelet production is under the control of humoral agents such as thrmbopoietin. They do not have nucleus and are bonded by a typical lipid bilayer membrane. Beneath the outer membrane lies the marginal band of microtubules which maintains the shape of the platelet and depolymerize when

aggregation begins. The cytoplasm has he following granules: the lysosomal granules, α granules and δ granules (Dacie & Lewis, 2002).

The platelet is one of the key elements of human blood.Platelets play a central role in the process of thrombus formation (thrombogenesis), as well as an important role in atherogenesis and the progression of atherosclerotic lesions. The interaction of the platelet with the vessel wall and its subsequent contribution to atheroma formation and thrombosis is of pivotal importance in the aetiology and pathogenesis of peripheral, coronary, cerebrovascular and other vascular diseases (Falk & Fernandez-Ortiz, 1995).

Platelet function in Haemostasis

Primary haemostasis begins when platelets adhere to site of endothelial disruption, leading to platelet clumping. This is followed by platelet activation, where the blood vessels walls exposes sub endothelium proteins, most notably von Willebrand factor (Vwf), present under the endothelium. vWF is a protein secreted by healthy endothelium, forming a layer between the endothelium and underlying basement membrane. When the endothelium is damaged,

The normally-isolated, underlying vWF is exposed to white blood cells and recruits factor VIII, collagen, and other clotting factors. Circulating platelets bind to collagen with surface collagen-specific glycoprotein Ia/IIa receptors. This adhesion is strengthened further by additional circulating proteins Vwf, which forms additional links between the platelets glycoprotein Ib\IX\V and the collagen fibrils. These adhesions activate the platelets (Kamath *et al.*, 2001). Activated platelets release the contents of stored granules into blood plasma. The granules include ADP, serotonin, platelet-activating factor (PAF), Vwf, platelets factor 4, and thromboxane A2 (TXA2), which in turn activate additional platelets. The granules' content activates a Gq-linked protein receptor cascade, resulting in increased calcium concentration in the platelets' cytosol (Gachet & Cazenave, 1991). The calcium activates protein kinase C, which, in turn, activates phospholipase A2 (PLA2). PLA2 then modifies the integrin membrane glycoprotein IIb/IIIa, increasing its affinity to bind fibrinogen. The activated platelets change shape from spherical to stellate, and the fibrinogen cross-links with glycoprotein IIb\IIIa aid in aggregation of adjacent platelets (completing primary haemostasis) (Pack ham, 1994; Dacie & Lewis 2002).

There are normally between 150-450 x 10^9/1 platelets in each microlitre of blood (Dacie & Lewis,2002).

Prothrombin time (PT)

Prothrombin time (PT) is a blood test that measures how long it takes blood to clot. It is also used to check for bleeding problems and to check whether medicine to prevent blood clots is actually working. The prothrombin time was discovered by Dr Armand Quick and colleagues in 1935, and a second method was published by Dr paul Owren, also called the ''p and p'' or ''prothrombin and proconvertin'' method (Quick *et al.,* 1935). The INR was a introduced in the early 1980's when it turned that there was large degree of variation between the various prothrombin time assays, a discrepancy mainly due to problems with the purity of the thromboplastin (tissue factor) concentrate (Hirsh & Bates, 2001).

The prothrombin time was developed to measure prothrombin (factor II) and hence its name. However, it subsequentiy became clear that it was sensitive to abnormalities of factors VII, X, V, II and fibrinogen (Horsli *et al.,* 2005).

Blood clotting factors are needed for blood to clot (coagulation). Prothrombin, or factor II, is one of the clotting factors made by the liver. Vitamin K is needed to make prothrombin and other clotting factors. One of the final steps of the cascade is the conversion of prothrombin (factor II) to thrombin. The PT test valuates the integrated function of these coagulation factors that comprise the extrinsic and common pathway of the coagulation cascade, including factor I (fibrinogen), II (prothrombin), V, VII and X. It evaluates the body's ability to produce a clot in a reasonable amount of time and, if any of thee factors are deficient (Horsti *et al.,* 2005).

The PT test is usually measured in seconds and is compared to values in healthy individuals. Because the reagents used to perform the PT test vary from one laboratory to another and even within the same laboratory over time, the normal values also will

fluctuate. To standardize result across, the World Health Organization (WHO) committee developed and recommended the use of the International Normalized Ratio (INR) with PT test for patients who are receiving the blood-thinning medication. This is due the difference between different batches of manufactured tissue factor used in the reagent to

perform the test. INR was devised to standardize the results. Each manufacturer assigns an ISI value (international sensitivity index) for any tissue factor they manufacture. The ISI values indicate how a particular batch of tissue factor compares to an internationally standardized sample. The ISI is usually between 1.0 and 2.0. The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system used. The INR became widely accepted worldwide, especially after endorsement by the world Health Organization.

Activated partial thromboplastin time (APTT)

The APTT in contrast to the PT measures the activity of the intrinsic and common pathways of coagulation. The division of the clotting cascade into the intrinsic, extrinsic and common pathways has little in vivo validity but remains a useful concept for interpreting the results of laboratory investigations.

The term 'thromboplastin' in this test refers to the formation of a complex formed from various plasma clotting factors which converts prothrombin to thrombin and the subsequent formation of the fibrin clot. The term 'Activated Partial Thromboplastin Time (APTT) drives from the original form of the test (devised in 1953) in which only the phospholipids concentration of the test was controlled (as opposed to the phospholipids and the surface activator concentrations) and the name 'partial thromboplastin' was applied at the time to phospholipids preparations which accelerated clotting but did not correct the prolonged clotting times of haemophilic plasma. Essentially the term 'partial' means phospholipid is present but no tissue factor.

The APTT is also known as Kaolin Cephalin Clotting Time (KCCT). The APTT evaluates the coagulation factors XII, XI, IX, VII, X, V, II (prothrombin), and I (fibrinogen) as well as prekallikrein (PK) and high molecular weight Kininogen (HMWK).

APTT may be ordered along with other tests such as a PT when a person presents with unexplained bleeding or bruising, a thromboembolism, an acute condition such as disseminated intravascular coagulation (DIC) that many cause both bleeding and clotting as factors are used up at a rapid rate, or with a chronic condition such as liver disease. When someone has had a thrombotic episode or recurrent miscarriages, the APTT may be ordered as part of an evaluation for lupus anticoagulant or anticardiolipin antibodies.

Fibrinogen

Fibrinogen is a soluble plasma glycoprotein protein produced in the liver by hepatocytes. It is a large molecule, made up of two identical halves, each half composed of three protein chains (α alpha, β beta, and Y gamma). The genes for these proteins are located on chromosome 4. The N-terminal sections of these three chains contain the cysteines that participate in the cross-linking of the chains. The C-terminal parts of α, β and Y chains contain a domain of about 225 amino-acid residues, which can function as a molecular recognition unit. In fibrinogen as well as in angiopoietin, this domain is implicated in protein-protein interactions. In lectins, such as mammalian ficolins and invertebrate tachylectin 5A, the fibrinogen C-terminal domain binds carbohydrates. On the fibrinogen α and β chains, there is a small peptide sequence (called a fibrinopeptide). These small peptides are what prevent fibrinogen from spontaneously forming polymers with itself (Hermans & McDonagh, 1982). Thrombin cleaves fibrinogen with the release of fibrinopeptides A and B, producing fibrin monomer which then polymerizes and is stabilized by the action of factor XIII. This is achieved through processes in the coagulation cascade that activate the zymogen prothrombin to the serine protease thrombin, which is responsible for converting fibrinogen into fibrin. Fibrin is then cross linked by factor XIII to form a clot. FXIIIa stabilizes fibrin further by incorporation of the fibrinolysis inhibitors alpha-2-antiplasmin and TAFI (thrombin activatable fibrinolysis inhibitor, procarboxypeptides B), and binding to several adhesive proteins of various cells (Muszbek *et al.*, 2008). Both the activation of Factor XIII by thrombin and plasminogen activator (t-PA) are catalyzed by fibrin (Muszbek *et al.*, 2008). Fibrin specifically binds the activated coagulation factors factor Xa and thrombin and entraps them in the network of fibers, thus functioning as a temporary inhibitor of these enzymes, which stay active and can be released during fibrinolysis. Fibrinogen also plays a role in normal platelet aggregation (Acharga & Dimichele, 2008).

In its natural form, fibrinogen can form bridges between platelets, by binding to their GpIIb/IIa surface membrane proteins.

Fibrinogen plays an important role in fibrin clot formation, factor XIIIa mediated fibrin cross-linking, platelet aggregation and fibrinolysis (Schneider *et al.*, 1999).

Fibrinogen abnormalities may be:

1. Absence of fibrinogen:- Hereditary afibrinogenemia (absence of fibrinogen, the homozygous state).
2. A decreased level of fibrinogen with normal structure:- hypofibrinogenemia (the heterozygous state, levels about half normal)
3. A structurally abnormal fibrinogen: - dysfibrinogenemia (hereditary or acquired).

Because fibrinogen is an acute phase reactant, elevated levels are frequently seen in inflammatory disorders, pregnancy, or after surgery, it also augments the deregulation of platelets in response to adenosine diphosphate (ADP), when taken up by α granules.

Higher levels are, amongst others, associated with cardiovascular disease. It may be elevated in any form of inflammation, as it is an acute-phase protein. It is used in veterinary medicine as an inflammatory marker.

Low levels of fibrinogen can indicate a systemic activation of the clotting system, with consumption of clotting factors faster than synthesis. This excessive clotting factor consumption condition is known as disseminated intravascular coagulation or DIC (DotevaII, 1994).

However, knowledge about the precise determinants of plasma fibrinogen levels in health and disease is as yet incomplete, and many paradoxes are still present. For example, it is known that plasma fibrinogen is higher in Black than in White patients, (Folsom *et al.*, 1992) but (in the UK at least) coronary artery disease is less common in Blacks than in White patients, while hypertension and stroke are conversely more common. Plasma fibrinogen is also influenced by many factors: it increases with age, body mass index, smoking,diabetes and post menopause and is related to fasting serum insulin, low-density-lipoprotein (LDL) cholesterol lipoprotein (a) and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical activity, increased high-density-lipoprotein (HDL) cholesterol, and with hormone replacement therapy (HRT) (DotevaII, 1994).

This acute phase proteins (fibrinogen) which is seen in an elevated levels in pregnancy (Stirling *et al.*, 1984; Ekaterina & Ilija, 2005; Hellgren, 2003), are also frequently seen in inflammatory state. HIV infection being an inflammatory state interacts with leucocytes through the surface receptors of the latter termed 'integrins'. The 2 main receptors for fibrinogen on the surface of leukocytes include Mac-1 (CDIIb/CD18, alpha M beta 2) and alpha X beta 2 (CDIIc/CD18, p150,95). Leukocytes (both monocytes and myelocytes) can specifically induce MAC-1 receptor to bind fibrinogen. Fibrinogen is also involved in the facilitation of both cell-cell interaction and the interaction of cell and extraccellualr matrix such as collagen. Thus, as explained above, fibrinogen is an important mediator of cell-cell interaction, adhesion and inflammation (Duperray *et al.*, 1997; Romero *et al.*, 2007).

CD4 Cells and CD4 Count

CD4 (Cluster of differentiation 4) is a glycoprotein expressed on the surface of T helper cells, monocytes, macrophages, and dendritic cells. It was discovered in the late 1970s and was originally known as leu-3 and T4 (after the OK T4 monoclonal antibody that reacted with it) before being named CD4 in 1984. In humans the CD4 protein is encoded by the CD4 gene. (Ryu *et al.*, 1994).

CD4 is a member of the immunoglobulin super family. It has four immunoglobulin domains (D_1 to D4) that are exposed on the extraccellualr surface of the cell. D1 and D3 resemble immunoglobulin variables (1gv) domains while D2 and D4 resemble immunoglobulin constant (igc) domains. CD4 uses its D1 domain to interact with the β - - domain of MHC class II molecules. T cells expressing CD4 molecules (and not CD8) on their surface, therefore, are specific for antigens presented by MHC II and not MHC class 1 (they are MHC class II – restricted). (Miceli *et al.*, 1993). CD4 is a co-receptor that assists the T cell receptor (TCR) with an antigen presenting cell. Using its portion that resides inside the T cells, CD4 amplifies the signal generated by the TCR by recruiting an enzyme tyrosine kinase, which is essential for activating many molecules involved in the signaling cascade of an activated T cell. CD4 also interacts directly with MHC class II molecules on the surface of the antigen. Presently cells using its extracellular domain (Barber *et al.*, 1989). HIV-1 uses CD4 to gain entry into host T-cells and achieves this by binding of the viral envelope protein known as glycoprotein 120 (gp120) to CD4. The binding to CD4 creates a shift in the conformation of gp120 allowing HIV-1 to bind to a co-receptor expressed on the host cell. These co-receptors are chemokinase receptors CCR5 or CXCR4) which of these co-receptors is used during infection is dependent on whether the virus is infecting a macrophage or T-helper cell (Kwong *et al.*,

1998). Following a structural change in another viral protein (gp41), HIV inserts a fusion peptide into the host cell that allows the membrane of the virus to fuse with the cell membrane. (Geyer *et al.,* 2001).

HIV infection leads to a progressive reduction in the number of T cells expressing CD4. Medical professionals refer to CD4 count to decide when to begin treatment during HIV infection. Normal blood values are 500-1200 $X10^6$/L. CD4 count test measures the number of T cells expressing CD4. Results are usually expressed as the number of cells per microliter (or cubic milliliter, mm^3) of blood. While CD4 tests are not a direct HIV test (does not check the presence of viral DNA or specific antibodies against HIV), it is used to assess the immune system of patients. Patients often undergo treatments when the CD4 count reach a level of 350 cells $X10^6$/L, less than 200 cells $X10^6$/L in a HIV positive individual is diagnosed as AIDs. Medical professionals also refer to CD4 tests to determine efficacy of treatment (Leavitt *et al.,* 2004).

The CD4 percentage is the percentage of the lymphocyte population that is CD4+; it is measured directly by flow cytometry. A CD4 percentage of <14% is considered to correspond to the same degree of immunosuppression as an absolute CD4 count of <200 cells/μL. The absolute CD4 count is calculated from the CD4 cell percentage and the total white blood cell count. The normal values for CD4 count varies considerably among different laboratories. The mean normal value for most laboratories is approximately 500-1,300 cells/μL. This calculated value is subject to more fluctuations than the CD4 cell percentage (Bofill *et al.,* 1992). Illness, vaccination, diurnal variation, laboratory error, and some medications can result in transient CD4 cell count changes, whereas the CD4 percentage remains more stable. Because CD4 counts may, vary, treatment decisions generally should not be made on the basis of a single CD4 value. When results are inconsistent with previous trends, tests should be repeated, and treatment decision usually should be based on two or more similar values. A change between two test results is considered significant if it is a 30% change in absolute CD4 count or 3 percentage point change in CD4 percentage. (Hogg, *et al.,* 2001)

In persons with untreated HIV infection, the CD4 count declines by approximately 50-80 cells/ μL. Per year, on average. The pattern of decline may be slow and steady, or the CD4 count may level off for an extended period of time (as in long-term nonprogressors) and then decrease. Although it takes an average of 10 years for a newly infected person to progress to AIDS, there is great variation among patients. For some patients, disease progression occurs within couples of years. For others, it takes more than 20 years, and a small number of patients appear to maintain high CD4 counts and undectable HIV RNA levels without ART (Pallela *et al.,* 2003)

Among asymptomatic individuals, the CD4 count typically is the major factor that guides the decision to initiate therapy, though the trend in recent years has been to treat willing individuals even at very high CD4 levels. Clinical status, viral load, pregnancy, comorbidities, and patient adherence to medications are among the other factors that should be taken into consideration (Shacker *et al.,* 1998).

Prophylaxis against opportunistic infections is based on CD4 count, and sometimes on CD4 percentage. For example, a CD4 count of <200 cells/ μL or a CD4 percentage of <14% is an indication for prophylaxis against pneumocystis carinii pneumonia; a CD4 count of <50 cells/ μL is an indication for prophylaxis against mycobacterium avium complex. The CD4 count also guides decision making in determining when to stop prophylaxis against opportunistic infections with patients whose CD4 counts rise in response to ART (Rudd *et al.,* 2010).

Effective ART typically results in CD4 count increases of >50 cells/ μL within weeks after viral suppression, and increases of 50-100 cells/ μL per year thereafter. For some patients who are older (age>50 years) and those with lower baseline CD4 cell counts are more likely to have blunted CD4 count responses. For monitoring purposes, the CD4 count should be repeated approximately every 3-6 months both in stable untreated patients and in patients on ART (for patients on ART with persistently suppressed HIV RNA and CD4 counts solidly above thresholds for opportunistic infection risk, current guidelines suggest monitoring every 6-12 months). The CD4 count should be checked more frequently if clinically indicated (e.g., switching therapy, ART failure, rapidly declining CD4 count) (US department of health and Human services, 2011).

Coagulation system and HIV infection

A number of coagulation abnormalities have been described in HIV disease including acquired deficiency states of the physiologic anticoagulants: protein C protein S and heparin cofactor II. Of these, protein S deficiencies are the most consistently

observed and is present in up to 73% of HIV infected men. Most commonly there is reduction in free protein S and coordinate reduction in functional protein S activity. Protein S is reduced in numerous other conditions including pregnancy, use of oral contraceptives, DIC, acute thrombosis and liver diseases. The clinical significance of acquired protein S deficiency associated with HIV disease is unclear. High levels of plasma von Willebrand factor have been reported in HIV disease and might be indicative of a activated endothelium.

Coagulation abnormalities associated with HIV infection are frequently encountered .The most common is the lupus anticoagulant, which is one of the several antibodies to acidic phospholipids that can occur as a result of the abnormal immune responses seen with HIV infection (Muhammad *et al.,* 2001).

An incidence of 20-66% has been reported for the lupus anticoagulant in patients with HIV infection (Gold *et al.,* 1986). The IgG or IgM antibody titer increases with active opportunistic infections.

The presence of this anitphospholipid antibody is established by the use of APTT. Elevation in the APTT is a most common abnormality (Bloom *et al.,* 1986).

Anticardiolipin antibodies (aCl) and lupus anticoagulants (LA) are frequent incidental laboratory findings in HIV-infected patients. The presence of LA is an established risk factor for both venous and arterial thrombosis in patients with SLE and is detected by a prolonged partial thromboplastin time (APTT) that fails to correct with mixing, or alternatively by prolongation of the Kaolin clotting time, diluted tissue thromboplastin time or dilute Russell viper venom time. Elevated aCL are found in 20-70% of HIV patients and are predominantly IgG La activity is prevalent in HIV-Infected patients and consists mainly of IgM antbody (Sahud *et al.,* 2002)

HIV infection has been recognized as a prothrombotic condition and this association has now been proven by a large number of studies with a reported VTE frequency among HIV-Infected patients ranging from 0.19% to 7, 63% HIV infection is associated with a two to tenfold increased risk of venous thrombosis in comparison with a general population of the same age. Some risk factors demonstrated a strongest association with VTE such as, low CD4 cell count especially in the presence of clinical AIDS, protein S deficiency, and protein C deficiency. Thrombosis during HIV infection was commonly vein thrombosis, arterial thrombosis is also more and more described the authors reported two cases of great trunks' arterial thrombosis in patients who are HIV infected for several months. Probable etiology is clearly carotid atherosclerosis associated with protein S deficiency in the fist case and antiphospholipid syndrome in the second case (Konin *et al.,* 2011)

The novel association of fibrinogen with HIV infected individual is noteworthy. Fibrinogen is a coagulation protein that is thought to play a major role in platelet aggregation and thus in creases in HIV infection. Interestingly, fibrinogen is increased in smokers and smoking is highly prevalent among HIV infected individuals (Phyllis *et al.,* 2010).

HIV Infections and Platelets

An association between the acquired immunodeficiency syndrome (AIDS) and CITP was described before the human immunodeficiency virus (HIV) has been isolated and characterized. HIV infects CD4 thymic lymphocytes, monocytes, macrophages and megakaryocytes. Although a number of different mechanisms have been reported by which HIV infection can produce thrombocytopenia, the ability of effective antiretroviral therapy to improve platelet counts demonstrates the relationship between viral replication and expression of viral-related proteins and the host response to platelets (Ballem *et al*., 1992). Thrombocytopenia was first associated with the acquired immune deficiency syndrome before the discovery of the HIV prior to the use of highly active antiretroviral therapy (HAART), HIV –associated thrombocytopenia (HIV-CITP, platelet count <150 X 10^9/L) was identified in approximately 5% to 30% of patients infected with HIV -1 Thrombocytopenia is more prevalent in patients with advanced HIV infection defined as a CD4 lymphocyte count of <200/µL, clinical AIDS, and among intravenous drug abusers. In the Multicenter AIDS Cohort Study of 1611 HIV –seropositive homosexual and bisexual men a platelet count of <150 x10^9/L) was reported in 6.7% of HIV –seropositive men. The incidence of thrombocytopenia was only 2.8% in men with CD4 lymphocyte counts greater then 700µL), but rose to 10.8% in those with CD4 lymphocyte counts of less than 200 µL. a review of 1004 patients who were HIV antibody positive seen in two HIV/AIDS clinics identified platelet counts of <150 x10^9/L) on at least one determination in 110 (11%) patients, 42 (4.2%) patients had platelet counts of >100x10^9/L and 15

(1.5%)had a platelet count of <150 x10^9/L) Thrombocytopenia was more prevalent in patients with a clinical diagnosis of AIDS (21.2%) and a CD4 lymphocyte count of less than 200 µL (20%) (Sloand *et al.*,1992).

A review of the medical records of 36,515 patients infected with HIV who were participants in the Multistage Adult and Adolescent spectrum of Disease project reported a 1-year incidence of thrombocytopenia of 3.7% defined as a platelet count of less than 50 x10^9/L. The incidence and severity of thrombocytopenia was associated with the stage of disease with an incidence of 1.7% among patients with HIV infection, but not clinical or immunologic AIDS, 3.1 % among persons with immunologic AIDS (CD4 lymphocytes < 200 µL) and 8.7% in patients with clinical AIDS by logistic regression analysis, clinical AIDS, CD4 lymphocyte count of <200 µL), age > 45 years, intravenous drug use, lymphoma and/or anemia was associated with a platelet count <50 x10^9/L (Sullivan *et al.*, 1997).

An increased incidence and severity of thrombocytopenia in HIV –infected intravenous drug users compared to HIV infected homosexuals has been reported Mientjes et al reported a platelet count of <150 x10^9/L in 29 of 182 (15.9%) homosexual HIV infected men compared with 38 of 181 (21%) HIV-infected intravenous drug users. None of the homosexual men had a platelet count of <50 x10^9/L, while 6 (3.3%) of intravenous drug users has a count of <50 x10^9/L. These differences may be explained, in part, by the higher incidence of co-infection with hepatitis C and underlying liver disease in HIV-infected intravenous drug users.

Multiple mechanisms may contribute to the development of CITP in the HIV-Infected patient and these have recently been reviewed. Proposed mechanisms include accelerated platelet clearance due to immune complex disease, and antiplatelet glycoprotein antibodies and/or anti-HIV antibodies that cross-react with platelet membrane glycoprotein's (antigenic mimicry). The ability of the HIV-1 to rapidly mutate may facilitate both its ability to escape immune surveillance and to mimic host antigens. Direct infection of megakaryocytes results in defective platelet production and megakaryocytic apoptosis. In this regards it is surprising that only a small percentage of patients infected with HIV develop clinically significant thrombocytopenia (Liebman & Stasiu, 2007).

Epidemiologic studies suggest that the pathogenesis of thrombocytopenia is partially dependent on disease burden. HIV associated thrombocytopenia developing early after infection more often resembles classical ITP in which thrombocytopenia is mediated primarily by peripheral destruction, whereas thrombocytopenia in patients with immunologic AIDS (CD4 lymphocytes < 200/ µL) is attributable predominately to decreased platelet production and ineffective hematopoiesis. While platelet counts may improve with antiretroviral therapy in both patient populations, patients with advanced disease are less likely to responded to classic primary CITP therapy such as splenectomy, corticosteroids, intravenous immunoglobulin or anti-RhD (Skaguchi *et al.*, 1991).

Initial studies of HIV-CITP suggested an immune complex mechanism was responsible for the thrombocytopenia, wherein platelets were cleared from the circulation as "innocent bystanders. More recent studies have shown that these immune complexes contain antibodies that cross-react with both HIV and platelet glycoprotein's. These antibodies also cross reacted with sequences on HIV nef, gag envc and pol proteins. Similar crossreactivity between HIV viral proteins and platelet glycoprotein's has been reported in the studies of Bettlaieb and co-workers immunoglobulin in platelet eluates bound to epitopes common to platelet GPIIIa and GP160.

Studies of platelet kinetics have demonstrated that HIV-CTIP is frequently associated with decreased platelet production. Megakaryocytes express the cd4 receptor and co-receptors necessary for HIV infection. Cytopathic infection of HIV of the megakaryocytes has been demonstrated and is the postulated primary mechanism for impaired plateletpoiesis (Ballem *et al.*, 1992).

Conclusion

A number of coagulation abnormalities have been described in human immunodeficiency virus (HIV) disease. High levels of plasma von Willebrand factor have been reported in HIV disease and might be indicative of activated endothelium. Endothelium is involved in important homeostatic mechanisms of non-thrombotic vascular surfaces, vascular tone regulation and immunomodulation. Injured endothelium leads to localized inflammatory response of which the direct consequence is the occurrence of occlusive thrombosis events mediated between leucocyte recruitment and platelet adhesion and aggregation, blood clothing activation and fibrinolysis

derangement. HIV infection has been associated with endothelial dysfunction. Since HIV infection is associated with endothelial dysfunction it may therefore result in activation and consumption of coagulation factors and ultimately coagulation defect.

References

Acharga, S.and Dimichele, D., M., (2008)."Rare inherited disorders of fibrinogen". *Haemophilia: the Official Journal of the World Federation of Haemophilia;* 14 (6):1151-1158.

Altman, L., W., (1982). New homosexual disorder worries officials. *The Nevy times.*

Anzala, O., A., Nagelkerke, N., J., Bwayo, J., J., Holton, D., Moses, S., Ngugi, E., N., Ndinya-Achola, J., O., Plummer, F., A., (1995). Rapid progression to disease in African sex workers with HIV-1 infection. *Journal of Infectious disease*; 171(3): 686-689.

Ascher, M., S., Sheppard, H., W., (1990). AIDS as immune system activation. *J. Acquired Immune Deficiency Syndromes*; 3: 177.

Baker, F., J, Silverton, R., E.and Pallister, C., J., (2007). Haemaostasis in Introduction to Medical Laboratory Technology. 7th ed, Honeyland Resources limited. PP 387.

Ballem, P., J., Belzberg, E., Devine, D., V., (1992). Kinetic studies of the mechanism of thrombocytopenia in patients with human immunodeficiency virus infection. *N Engl J Med*; 327: 1779-1784.

Barber, E., K., Dasgupta, J., D., Schlossman S., F., Trevillyan, J., M., Rudd, C., E., (1989). "The CD4 and CD8 antigens are coupled to a protein-tyrosine kinase (p56lck) that phosphorylates the CD3 complex".*Proc. Natl. Acad. Sci*; 86(9): 3277-3281.

Barre-sinouss, F., Chermand, J., C., Ray, F., (1983). Isolation of a lymphotropic retrovirus from a patient at risk for AIDS. *Science*; 220 (4599): 868-871.

Bloom, E., J., Abrams, D., L., Rodgers, G., M., (1986). Lupus anticoagulant in AIDS. *JNAA*; 256: 491-493.

Bobkor, A., F., Kazennoa, G., V., Selomeva, L., M., (2004). LemporII trends in the HIV-1 epidemic in Russia, predominance of subtype A. *I.Med Virol*; 74(2): 191-196.

Bofill, M., Janossy, G., Lee, C., A., MacDonald-Burns, D., Philips A., N., Sabin, C., Timms, A., Johnson, M., A., Kernoff P., B., (1992). "Laboratory control values for CD4 and CD8 T lymphocytes. Implications for HIV-1 diagnosis." *Clin. Exp. Immunol*; 88(2): 243-252.

Boily, M., C., Baggeley, R., F., Wang, L., Masse B., White R., G., Heyes R., J., Alary, M., (2009). Heterosexual risk in HIV-1 infection per sexual act: systematic review and metaanalysis of observational studies. *The infectious diseases*; 9(2): 118-129.

Campbell, G., R., (2004). "The glutaminerich region of HIV-1 fat protein involved in T cell apoptosis. *Journal of Biological Chemistry*; 279 (46): 48197-48204.

Centres for Disease Control and Prevention (2009). Guidelines for prevention and treastment of opportunistic infections in HIV-1 infected adults and adolescents: Recommendations from CDC, the national institutes of Health and the HIV medicine association of the infectious diseases society of America.

Cesarman-Maus, G., Hajjar, K., A., (2005). Molecular mechanisms of fibrinolysis. *British Journal of Haematology*; 129 (3): 307-321.

Cohan AJ, Philips TM, K essler CM, (1986). Circulating coagulation inhibitors And AIDs. *Ann. Intern. Med*, **104**: 175-180

Cotran, R., S., Kumar, V., Fausto, N., Nelson, F., Robbins, S., L., Abbas, A., K., (2005). Robins and Cotran pathologic basis of disease. St. Louis, Mo: Elsevier Saunders. Pp 125-126.

Dacie, J., V., Lewis, S., M., (2002). Investigation of haemostasis in practical haematology, 8th ed, Churchill living stone, London. Pp 383.

Dotevall, A., Johansson, S., Wilhelmsen, L., (1994). Association between fibrinogen and other risk factors for cardiovascular disease in men and women. Results from the Goteberg MONICA survey 1985. *Annals of Epidemiology*; 4:369-374.

Dovek, D., C., Roederer, M., Koup, R., A., (2009). Emerging concepts in the immunopathogenesis of AIDS. *Annu. Rev. Med*.; 60: 471-484.

Duperray, A., Languino, L., R., Plescia, J., McDowall, A., Hogg, N., Craig, A., G., Berendt, A., R., Altieri, D., C., (1997). Molecular identification of a novel fibrinogen binding site on the first on the first domain of ICAM-1 regulating leukocyte-endothelium bridging. *Biological Chemistry*; 272:435-441.

Ekaterina, H., U.and Illija, I., L., (2005). Changes in haemostasis during pregnancy. *European Journal of Obstetric Gynaecology and Reproductive Biology*; 119(2):185-188.

Esmon, C., T., (2003). The protein C pathway. *Chest Journal*; 124:26-27.

Falk E, Fernandez-Ortiz D, (1995). A. Role of thrombosis in atherosclerosis and Its complications. *Americal Journal of Cardiology*, **75**: 3-11

Fischi, M., A., Richman, D., D., Grieco, W., A., Gottlieb M., S., Volberding, P., A., Laskin O., L., Leedom, J., M., Groopman, J., E., Mildvan, D., Schooley, R., T., (1987). The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex, a double blind, placebo controlled trial. *N Engl J Med*; 317: 185-191.

Fox, C., H., Cottler-Fox, M., (1992). The pathology of HIV infection. *Immunol. Today*; 13: 353.

Furie, B., Furie, B., C., (2005). Thrombus formation in vivo. *J Chin Invest*; 115(12): 3355-3362.

Gatchet, C., Cazenave, J., P., (1991). ADP induced blood platelet activation: a review. *Nouvelle Revue Francaise D Haematologic*; 33:347-358.

Geyer, M., Fackler, O., T., Peterlin, B., M., (2001). "Structure-function relationships in HIV-1 Nef". *EMBO Rep*; 2(7):580-585.

Giangrande, P., L., (2003). "Six characters in search of an author: the history of the nomenclature of coagulation factors". *British Journal of Haematology;* 121(5): 703-712.

Gilbert, G., E., Arenna, A., A., (1997). Partial activation of the factor VIIIa-factor IXa enxyme complex by dihexanoic phosphatidylserine at submicellular concentration. *Biochemistry*; 36:1768-1769.

Gilbert, P., Mckeague, W., Eisen, G., Mullins, C., Gueye-Ndiaye, A., Mboup, S., Kanki, P., J., (2003). Comparison of HIV-1 & HIV-2 infectivity from a prospective cohort study in Senegal. Statistics in Medicine; 22(4): 573-593.

Gold, J., E., Haubenstock, A., Zalusky, P., X., (1986). Lupus anticoagulant and AIDS. *N Engl J Med*; 314: 1252-1253.

Goudsmit, J., (1997). Oral sex in: The nature of AIDS, Oxford University Press, New York. Pp 50-51.

Greenberg, D., L., Davie, E., W., (2001). Blood coagulation factors: their complimentary DNA,genes and expression. In: Coluan RW, Hiroh J, Marder VJ, Clower AW, George JN, (eds) *Haemostasis and thrombosis: Basic principles and clinical practice.* Pjiladelphia, PA: Lippincott Williams and Wilkins. Pp21-57.

Greene, W., C., (1991). The molecular biology of human immunodeficiency virus type 1 infection. *New Engl. J. Med*; 324: 308.

Hajjar, K., A., (1995). Cellular receptors in the regulation of plasmin generation. *Thrombosis and Haemostasis*; 74:294.

Hammer, S., M., Squires, K., E., Hughes, M., D., Greines, J., M., Demeter, L., M., Currier, J., S., Eron, J., J., Feinberg, J., E., Balfour, H., H., Deyton, L., R., Chodokewitz, J., A., (1997). A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200/mm^3 or less. AIDS clinical trial group 320 study study team. *N Engl J Med*; 337: 725-733.

Harrer, T., (1996). Strong cytotoxic T cell and weak neutralizing antibody responses in a subset of persons with stable non progressing HIV-1 infection. *AIDS research and Human retroviruses*; 12(7): 585-592.

Hellgren, M.,(2003). Hemostasis during pregnancy and puerperium. *Seminars in thrombosis and haemostasis;* 29(2): 125-130.

Hemelar, J., Gouws, F., Ghys, P., D., Osmanor, S., (1996). Global and regional distribution of HIV-1 genetic subtypes and recombinants. *AIDS*; 20(16): 13-23.

Henry, J., B., (2001). Clinical diagnosis and management by laboratory methods, 20th edition. Philadelphia: W.B Sanders Co. pp 128-130.

Hirsh, J., Bates, S., M., (2001). "Clinical trials that have influenced the treatment of venous thromboembolism: a historical perspective". *Annals of Internal Medicine*; 134(5): 409-417

Ho, D., D., Neumann, A., U., Perelson, A., S., Chen, W., Leonard, J., M., Markowtz, M., (1995).Rapid turnover of plasma virions and CD4 and lymphocytes in HIV-1 infection. *Nature*; 373: 123-126.

Hogg, R., S., Yip, B., Chan, K., J., (2001). Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA*; 286(20): 2568-2577.

Holmsen, H., (1994). Significance of testing platelet functions in vitro. *European journal of Clinical investigations*; 24:3-8.

Horsti, J., Uppa, H., Vilpo, J., A., (2005). " Poor agreement among prothrombin time international normalized ratio method". *Clinical Chemistry*; 51(3): 553-560.

Julie ,Y., Ruthie ,C., Ana vallaria, C. N., Dora,M., Ncaise, N., Lzare, k., lutz, G., Gurtler, P. B., Gerald, S., Sushil, G., Davare,and C.A (2006), Identification of HIV-1 group N infections in a husband and wife in Cameroon. *AIDs Research and Human Retroviruses* **22**(1): 82-92

Kamath, S., Blann, A., D., Lip, G., Y., H., (2001). Haemostasis, thrombosis and vascular biology. *European Heart Journal*; 22: 1561-1571.

Karpatkin, S., Nardi, M., Green, D., (2002). Platelet and coagulation defects associated with HIV-1 infection. *Thromb Haemost*; 88: 389-401.

Kher U (1982). A name for the plague.

Korber B, Muldoon M, Theiler J, Gaoif, Guptar R, Lapedes A, Hahn BH, Wolinsky S, (2000), Timing the ancestor of the HIV-1 pandemic strains, *Sci* **288** (5472): 1789-96.

Konin, C., Anzouan-Kacou, J., B., Essam N'loo, A., (2011). Arterial thrombosis in patients with Human immunodeficiency virus: Two-case reports and review of the literature. *Case reports in vascular medicine*; 1155(847241): 1-4.

Kuby, J., (1997). The immune system in AIDS. In Immunology: 3rd edition; Freeman and Company. Pp 523-541.

Kumaranyake, L., Watts, C., (2001). Resource allocation and priority setting of HIV/AIDS interventions; addressing the generalized epidemic in sub-sahara *Africa. J Int Dev*; 13(4): 451-466.

Kwong, P., D., Wyatt, R., Robinson, J., Sweet, R., W., Sodroski, J., Hendrickson, W., A., (1998). "Structures of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody". *Nature*; 393(6686): 648-659.

Leavitt, S., A., Schon, A., Klein, J., C., (2004). "Interactions of HIV-1 Nef with cellular partners define a novel alosteric paradigm". *Curr. Protein Pept. Sci*; 5(1):1-8.

Levy, J., A., (1993). HIV pathogenesis and long term survival. *AIDS*; 7(2): 141-150.

Liebman, H., A., (2008). Viral-associated Immune Thrombocytopenic purpura. *Hematology*; 60: 1-19.

Liebman, H., A., Stasi, R., (2007). Secondary immune thrombocytopenic purpura. *Curr Opin Hematol*; 14: 557-573.

Marx, P., A., Alcabes, P., G., Drucker, E., (2001). Serial human passage of siminan immunodeficiency virus by unsterile injections and the emergence of epidemic HIV in Africa. *Philos Tran T Soc Lond B Biol Sci*; 356: 911-920.

Masur, H., Michelis, M., A., Wormser, G., P., Lewis, S., Gold, J., Tapper, M., L., Giron, J., Lerner, C., W., Armstrong, D., Setia, U., Sender, J., A., Siegal, F., P., Cunnigham, R., S., (1982). Opportunistic infection in previously healthy women. Initial manifestations of a community acquired cellular immunodeficiency. *Ann Intern Med*; 97: 532-539.

Miceli, M., C., Parnes, J., R., (1993). "Role of CD4 and CD8 in T cell activation and differention". *Adv. Immunol*; 53: 59-122.

Morgan, D., C., Mahe, B., Mayanja, J., M., Okongo, R., L., Whitworth, J., A., (2002). HIV-1 infection in rural Africa. *AIDS*; 16(4): 597-603.

Morgan, D., C., Mahe, B., Mayanja, J., M., Whitworth, J., A., (2002). Progression to symptomatic disease in patients infected with HIV-in rural Uganda: prospective cohort study. *BMJ*; 324 (7331): 345-347.

Muhammad, W., S., Bernard, G., (2001). AIDS patient care and STDS. *AIDS*; 15(1): 15-24.

Musbek, L., Bagoly, Z., Bereczky, Z., Katona, E., (2008). "The involvement of blood coagulation factor XIII in fibrinolysis and thrombosis". *Cardiovascular and Hematological agents in Medicinal Chemistry*; 6(3):190-205.

Norris, I., A., (2003). Blood coagulation. *Best practice Research clinical Obstetrics and Gynaecology*; 17: 369-386.

Oldenburg, J., Bevans, C., G., Muller, C., R., Watzka, M., (2006). "Vitamin k epoxide reductase complex subunit 1 (VKORCI): the key protein of the vitamin K cycle". *Antioxidants Redox Signalling*; 8(34): 347-353.

Omoregie, R., Osakwe, S., I., Ihemeje, V., Omokaro, E., U., Ogefere, H., O., (2009). Correlation of CD4 count with platelet count, prothrombin time, activated partial thromboplastin time among HIV patients in Benin City, Nigeria. *West Indian Med. J*; 58(5): 1-9.

Packham, M., A., (1994). Role of platelets in thrombosis and haemostasis. *Canadian Journal of Physiology and Pharmacology*; 72: 278-284.

Pagana, K., D., Pagana, T., J.,(2006). Mosby's Manual Of Diagnostic and Laboratory tests. 3rd edition St. Louis: Mosby. Pp230-233.

Pallela, F., J., Delancy, K., M., Moorman, A., C., Loveless, M., W., Fuhrer, J., Satten, G., A., Holmberg, S., D., (1998). Declining morbidity and mortality among patients with advanced HIV, infect HIV outpatient study investigator. *New English Journal of Medicne*; 338(13): 853-860.

Pallella, F., J., Deloria-knoll, M., Chmiel, J., S., (2003). Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med*; 138(8): 620-626.

Pantaleo, G., Fauci, M., S., (1995). New concepts in the immunopathogenesis of HIV infection. *Annu. Rev. Immunol*.; 13: 487.

Peeters, M., Gueye, M., A., Bibollet-Ruche, F., Ekaza, E., Mulanga, C., Ouedrago, R., Gandji, R., Mpele, P., Dibanga, G., Badombena, W., Luo, N., Vanden, H., M., Delarporte, E., (1997). Geographical distribution of HIV-1 group O viruses in Africa. *AIDS*; 1(4): 493-498.

Phyllis, C., T., Andy, I., C., Andrew, R., Z., Constance, B., Russell, T., Rebecca, S., Peter, B., Michael, S., Carl, G., (2010). Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. *J Acquir Immune Defic Syndr*; 55(3): 316-322.

Plantier, J., C., Dickerson, J., E., De Oliveira, F., Cordonnier, F., Lemce, V., Damond, F., Robertson, D., R., Simon, F., (2009). HIV derived from gorillas. *Natural Medicne*; 15(8): 871-884.

Quick, A., J., Stanley-Brown, M., Bancroft, F., (1935). "A study of the coagulation defect in haemophilia and in jaundice". *American Journal of Medical Sciences*; 190: 501-502.

Ratner, L., Haseltine, W., Patarca, R., (1985). Complete nucleotide sequence of AIDS virus HTLV-III. *Nature*; 313(6000): 277-284.

Romero, R., Rosner, B., A., Williet, W., C., (200). Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and foetal injury.*Nutrition Reviews*; 2: 194-202.

Rudd, C., E., Trevillyan, J., M., Dasgupta, J., D., Wong, L., L., Schlossman S., F., (1988). "Pillars article: the CD4 receptor is complexed in detergent lysates to a protein-tyrosine kinase from human T lymphocytes". *J. Immunol*; 185(14): 2645-2649.

Ryu, S., E., Truneh, A., Sweet, R., W., Hendrickson, W., A., (1994). "Structures of an HIV and MHC binding fragment from CD4 as refined in two crystal lattices". *Structure*; 2(1): 59-74.

Safrit, J., T., Koup, R., A., (1995). The immunology of primary HIV infection: which immune responses control HIV replication? *Curr. Opin. Immunol*.; 7: 456.

Sahud, M., A., Claster, S., Liu, L., Ero, M., Harris, K., Furlan, M., (2002).Von Willebrand factor-cleaving protease inhibitor in a patient with human immunodeficiency syndrome-associated thrombotic thrombocytopenic purpura. *B J Haematol*; 116: 909-911.

Sakaguchi, M., Sato, T., Groopman, J., E., (1991). Human immunodeficiency virus infection of megakaryocytic cells. *Blood*; 77: 481-485.

Salami, M., (2000). Dating the common ancestor of siVeps and HIV-1 group M and the origin of HIV-1 sub types by using a new method to uncover clock like molecular evolution. *The FASEB Journal*; 15(2): 276-278.

Santiago, M., L., Range, F., Keele, B., F., Li, Y., Bailes, E., Bobollet-Ruche, F., Fruteau, C., Neo, R., (2005). HIV-2. *Journal of virology*; 79(19): 12515-12517.

Schneider, D., J., Taatjes, D., J., Howard, D., B., Sobel, B., E., (1999). Increased reactivity of platelets induced by fibrinogen independent of its binding to the IIb-IIIa surface glycoprotein: a potential contributor to cardiovascular risk. *Journal of American College of Cardiology*; 33: 261-266.

Shacker, T., W., Hughes, J., P., Shea, T., (1998). Biological and virologic characteristics of HIV infection. *Ann Intern Med*; 128(8): 613-620.

Shapiro, S., S., (2003). "Treating thrombosis in the 21st century" *New English Journal of Medicne*; 349(18): 1762-1764.

Sloand, E., M., Klein, H., G., Banks, S., M., Vareldzis, B., Merritt, S., Pierce, P., (1992). Epidemiology of thrombocytopenia in HIV infection. *Eur J Haematol*; 48): 168-172.

Sloand, E., M., Klein, H., G., Banks, S., M., Vareldzis, B., Merritt, S., Pierce, P., (1992). Epidemiology of thrombocytopenia in HIV infection. *Eur J Haematol*; 22(1): 83-92.

Smith, J., A., Daniel, R., (2006). Following the path of the virus the exploitation of host DNA repair mechanisms by retoviruses. *Chem Biol* ; 1 (4): 217-226.

Stirling, Y., Woolf, L., North, W., R., Seghatchian, M., J., Meade, T., W., (1984). Haemostatis in pregnancy. *Thrombosis and Haemostasis*; 52(2): 176-182.

Sullivan, P., S., Hanson, D., L., Chu, S., Y., Jones, J., L., Ciesielski, C., A., (1997). Surveillance for thrombocytopenia in persons infected with HIV: results from the multistate Adult and Adolescent spectrum of Disease project. *J Acquir immune Defic Syndr Hum Retrovirol*; 14: 374-379.

Takatoshi, K., Kenji, N., Shinichi, O., Megumi, S., Shinsaku, H (1994). Determination of tissue factor antigen and it's clinical significance. *British Journal of Haematology*; 87(2): 343-347.

Tolstrup, M., Ostergaard, L., Laursen, A., L., (2004). "HIV/SIV escape from immune surveillance: focus on Nef". *Curr. HIV Res*; 2(2):141-151.

Tortora, G., J., Grabowski, S., R., (1996). Principles of Anatomy and Physiology: 8th edition, Harper Collins, New York. Pp 236 -240.

U.S Department of Health and Human Services (2011). Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents.

Ukaejiofo, O., E., (2009). HIV/AIDS update in blood transfusion in the tropics, 2nd ed. Salem Media (Nig) Ltd. Pp 184 & 194.

Warn-Cramer, B., Roa, L., Maki, S., Rapaport, S., I., (1998). Modification of extrinsic pathway inhibitors (EPI) and factor Xa that affect their ability to interact and inhibit factor VII/tissue factor: Evidence for a two-step model of inhibition. *Thrombin Haemostasis*; 60:453-454.

Weiss, R., A., (1993). How does HIV cause AIDS. *Nature*; 460(7256): 711-716.

Wright, I., S., (1962). “The nomenclature of blood clotting factors”. *Canadian Medical Association Journal*; 86: 373-374.

Zhu, P., Liu, J., Bess, J., (2006). Distribution and three-dimensional structure of AIDS virus envelop spikes. *Nature*; 15(7095): 817-818.