ISSN 2348-0319 International Journal of Innovative and Applied Research [2022]
(Volume 10, Issue 05)
01-11

Journal home page: http://www.journalijiar.com

INTERNATIONAL JOURNAL
OF INNOVATIVE AND APPLIED RESEARCH

RESEARCH ARTICLE

A SYSTEMATIC REVIEW ON SOME COAGULATION PROFILE IN HIV INFECTION

Oladoyin Hellen Oloro[1] and Emmanuel Ifeanyi Obeagu[2]

1. Department of Medical Laboratory Science, Achievers University, Owo, Ondo State, Nigeria.
2. Department of Medical Laboratory Science, Kampala International University, Western Campus, Ishaka, Uganda.

Manuscript Info

Manuscript History
Received: 22 April 2022
Final Accepted: 19 May 2022
Published: 30 May 2022

Keywords:
Prothrombin Time, Thrombin, Thrombin Time Activated Partial Thromboplastin Time, HIV, Coagulation

Abstract

According to UNAIDS, there were approximately 37.9 million people across the globe with HIV/AIDS in 2018. Of these, 36.2million were adult and 1.7 million were children (<15years old). New HIV infection – An estimated 1.7 million individuals worldwide were newly infected with HIV in 2018.Blood coagulation abnormalities occur frequently in people infected with Human Immunodeficiency Virus (HIV). Researches so far shows the retrovirus is associated with endothelial dysfunction and liver damage. Both endothelial dysfunction and liver damage can result in coagulation defect because most coagulation factors are produced in the liver and some are activated by the tissues therefore default to them can lead to coagulation defect. It is therefore expected that as HIV progresses coagulation abnormalities increases. However, few studies showed the association of these abnormalities with antiretroviral therapy (ART). Prothrombin time (PT) and partial thromboplastin time with kaolin (PTTK) use to assess the extrinsic and intrinsic pathway respectively alongside with platelet count help to screen for coagulation abnormalities in HIV infected person. The intrinsic pathway comprising of factor I,II,IX,X,XI and factor XII while the extrinsic pathway comprising of factor I,II,V,VIII and factor X. HIV-related thrombocytopenia (Tr-HIV) is the most common haemostatic disorder with a high morbidity and affects patients from every risk group independently of age, sex, or stage of infection. Two mechanisms are responsible for the Tr-HIV: bone marrow failure and immunological disorders, namely, circulating immune complex deposited on the platelet membrane and the production of autoantibodies directed against platelets.

***Corresponding Author:-** **Emmanuel Ifeanyi Obeagu**

Introduction:-

HIV stands for Human Immunodeficiency Virus. It is a lentivirus (a member of retrovirus) that causes HIV infection and overtime Acquired Immunodeficiency Syndrome (AIDS).The virus spread through certain body fluid to attack the body immune cells that move around the body, detecting faults and anomalies in cells as well as infections. When HIV targets these cells, It allows life threatening opportunistic infection and cancer to thrive (Samjiet al., 2013; Igwe et al., 2022; Madekwe et al., 2022; Obeagu et al., 2017)

HIV infects vital cells in the human immune system, such as helper T cells (specifically CD4+T cells), macrophages, and dendritic cells. HIV cannot replicate on its own, so in order to make new copies of itself, it must

infect cells of the human immune system. CD4 cells are white blood cells that play a central role in responding to infections in the body. Over time, CD4 cells are killed by HIV and the body's ability to recognise and fight some types of infection begins to decline. If HIV is not controlled by treatment, the loss of CD4 cells leads to the development of serious illnesses, or 'opportunistic infections'. In people with normal CD4 cell levels, these infections would be recognised and cleared by the immune system (Brenchley et al., 2012; Oloro et al., 2022)

HIV causes low levels of $CD4^+$ T cells through a number of mechanisms, Pyroptosis of abortively infected T cells, apoptosis of uninfected bystander cells, and killing of infected $CD4^+$ T cells by $CD8^+$ cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections, leading to the development of AIDS (Brenchley et al., 2012).

HIV is called a retrovirus because it works in a back-to-front way. Unlike other viruses, retroviruses store their genetic information using RNA instead of DNA, meaning they need to 'make' DNA when they enter a human cell in order to make new copies of themselves.HIV is a spherical virus. The outer shell of the virus is called the envelope and this is covered in spikes of the glycoproteins gp120 and gp41, which allow HIV to lock onto the CD4 receptor on CD4 T cells and enter the cell (Liet al., 2016).

Inside the virus envelope is a layer called the matrix. The core of the virus, or nucleus, is held in the capsid, a cone-shaped structure in the centre of the virion. The capsid contains two enzymes essential for HIV replication, the reverse transcriptase and integrase molecules. It also contains two strands of RNA – which hold HIV's genetic material (Lyumkis et al., 2013).

HIV can be transmitted through body fluids that include blood, semen, vaginal, rectal fluids and breast milk of the infected person to HIV free person. The major routes of transmission are unsafe sex, contaminated sharp objects, and transfusion of contaminated blood, from infected mother to her child during pregnancy, childbirth, and breastfeeding. Within this fluid HIV is present as both free virus particles and virus within infected immune cells (Patel et al., 2014).

Experiencing a collection of these infections is the most advanced stage of HIV, which is when a person is also said to have AIDS (Acquired Immune Deficiency Syndrome). Effective testing and treatment of HIV means that the large majority of people living with HIV do not reach this stage (Maartenset al., 2014).

Antiretroviral therapy (ART) is the use of HIV medicines to treat HIV infection. People on ART take a combination of HIV medicines (called an HIV treatment regimen) every day. ART is recommended for everyone who has HIV. People with HIV should start ART as soon as possible. ART can't cure HIV, but HIV medicines help people with HIV live longer, healthier lives. ART also reduces the risk of HIV transmission. The main goal of ART is to reduce a person's viral load to an undetectable level. An undetectable viral load means that the level of HIV in the blood is too low to be detected by a viral load test. People with HIV who maintain an undetectable viral load have effectively no risk of transmitting HIV to their HIV-negative partner through sex. Although HIV can be controlled by antiretroviral therapy, it cannot be eliminated from the body (Kibaru, et al., 2015). This is because HIV evades the normal immune system mechanisms for getting rid of cells infected by viruses. HIV integrates itself into the DNA of human immune system cells and only replicates when the cell is stimulated to respond to an infection. These cells are called latently-infected cells. These cells are not recognised as infected by the immune system and killed off, allowing them to persist for as long as the cell lives (Ifeanyichukwuet al., 2012).

Coagulation profile include PT,PTTK, and Plateletcount. It is a screening test for abnormal blood clotting because it examines the factors most often associated with a bleeding problem. It does not cover all causes of bleeding tendencies. Coagulation testing are the tests used for diagnostics of the homeostasis system because it examines the observation of development of blood clot in blood and plasma. A coagulation profile is a blood test. It requires a few mililitres of blood from a vein, and it is important that the blood sample tube is filled to the correct level – otherwise false readings may occur (Winteret al., 2017).

A coagulation profile may be performed to confirm normal clotting function before a procedure which may cause bleeding, or in conditions associated with bleeding, for example from the respiratory, urinary, or gastrointestinal tract. It may also be requested by your doctor if there is a concern about easy bruising or bleeding. This may happen

because of hereditary conditions such as Haemophilia, or acquired conditions such as liver failure, or severe infections.A condition called Disseminated Intravascular Coagulation(DIC) may occur in critically ill patients, from a variety of possible causes. DIC affects all the components of the coagulation profile (Panova-Noeva et al., 2019).

Signs And Symptoms Of Hiv

Lopex et al. (2012) reported that the symptoms of HIV varies depending on the stage of infection. Though people living with HIV tends to be more infectious in the first few months after being infected, many are unaware of their status until the later stages. In the first few months after initial infection people may experience no symptoms or an influenza-like illness including

Fever
Headache
Rash or sore throat

As the infection progressively weakened the immune system, they can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea and cough. Without treatment, they could also develop severe illness such as

Tuberculosis,
Cryptococcal
|Meningitis,
Severe bacterial infection and
Cancer such as lymphomas and kaposi's sarcoma.

Transmission Of HIV

HIV is transmitted via the exchange of variety of body fluids from infected person, such as blood, breast milk, semen and vaginal secretions. HIV and also be transmitted from mother her child during pregnancy or delivery. Individual cannot become infected through ordinary day to day contact such as kissing, hugging, shaking hands, or sharing personal objects, food and water (Patel et al., 2014).

The Life Cycle Of HIV

1. **Attachment and Entry**- The process of producing new viruses begins when HIV gains entry to a cell. This process happens in two stages, attachment and fusion. When HIV makes contact with a CD4 cell, the gp120 spikes on the surface of HIV lock onto the CD4 receptor and another co-receptor, either CCR5 or CXCR4.The gp41 protein is used to fuse the HIV envelope with the cell wall. This process of fusion allows the HIV capsid to enter the CD4 cell. Several types of antiretroviral drug have been developed to block different stages of the processes of attachment and entry:

- CCR5 inhibitor
- Attachment inhibitor
- Fusion inhibitor

The gp41 and gp120 proteins on the surface of the virus are also targets for vaccines that are designed to produce antibody responses. (Zhou et al., 2010).

2. **Reverse transcription** - When HIV RNA enters the cell it must be `reverse transcribed` into proviral DNA before it can be integrated into the DNA of the host cell. HIV uses its reverse transcriptase enzyme to convert RNA into proviral DNA inside the cell.

Two types of antiretroviral drug have been developed to stop the action of reverse transcriptase and the creation of proviral DNA:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs and NtRTIs) block HIV production by inserting a nucleoside or nucleotide into the chain of HIV DNA as it is created, terminating the chain.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) block HIV production by binding directly to the reverse transcriptase enzyme (Zhou et al., 2010).

3. Integration-

After HIV RNA is converted into DNA, HIV's integrase enzyme attaches itself to the end of the proviral DNA strands and it is passed through the wall of the cell nucleus. Once the proviral DNA enters the cell nucleus, it binds to the host DNA and then the HIV DNA strand is inserted into the host cell DNA. HIV integrase inhibitors have been developed to block the transfer of the HIV DNA strand into the host cell DNA. After the proviral DNA is integrated into the DNA of the host cell, HIV remains dormant within the cellular DNA. This stage is called latency

and the cell is described as 'latently infected'. It can be difficult to detect these latently infected cells even when using the most sensitive tests (Zhou et al., 2010).

4. Transcription and Translation-

The cell will produce HIV RNA if it receives a signal to become active. CD4 cells become activated if they encounter an infectious agent. When the cell becomes active, HIV uses the host enzyme RNA polymerase to make messenger RNA. This messenger RNA provides the instructions for making new viral proteins in long chains. The long chains of HIV proteins are cut into smaller chains by HIV's protease enzyme (Zhou et al., 2010).

5. Assembly and budding-

These protein chains begin to assemble into new viruses at the cell wall.

- HIV protease inhibitors are designed to block the activity of HIV's protease enzyme.

As the virus buds from the cell wall, its genome becomes enclosed in a capsid produced from HIV's gag protein. After the new virus is assembled, it must leave the cell by pushing through the cell wall. To leave the cell completely and become infectious, the virus must take lipids (fats) from the cell wall to make the surface glycoproteins.

- Maturation inhibitors are being developed to block the cutting of the gag protein that is needed to produce a mature virus (Zhou et al., 2010).

Haemostasis

Hemostasisis the cessation or arrest of blood from a damaged vessel followed by repair. It is a process to prevent and stop bleeding, meaning to keep blood within a damaged blood vesselthe opposite of haemostasis is haemorrhage (Shen et al., 2017). It is the first stage of wound healing. This involves coagulation, blood changing from a liquid to a gel. Intact blood vessels are central to moderating blood's tendency to form clots. The endothelial cells of intact vessels prevent blood clotting with a heparin-like molecule and thrombomodulin and prevent platelet aggregation with nitric oxide and prostacyclin. When endothelial injury occurs, the endothelial cells stop secretion of coagulation and aggregation inhibitors and instead secrete von Willebrand factor (factor VIII) which initiate the maintenance of haemostasis after injury. Haemostasis has three major steps:

1) Vasoconstriction,
2) Temporary blockage of a break by a platelet plug,
3) Blood coagulation, or formation of a fibrin clot. These processes seal the hole until tissues are repaired (Grover et al., 2019).

Haemostasis occurs when blood is present outside of the body or blood vessels. It is the innate response for the body to stop bleeding and loss of blood. During haemostasis three steps occur in a rapid sequence. Vascular spasm is the first response as the blood vessels constrict to allow less blood to be lost. In the second step, platelet plug formation, platelets stick together to form a temporary seal to cover the break in the vessel wall. The third and last step is called coagulation or blood clotting. Coagulation reinforces the platelet plug with fibrin threads that act as a "molecular glue". Platelets are a large factor in the haemostatic process. They allow for the creation of the "platelet plug" that forms almost directly after a blood vessel has been ruptured. Within seconds of a blood vessel's epithelial wall being disrupted platelets begin to adhere to the sub-endothelium surface. It takes approximately sixty seconds until the first fibrin strands begin to intersperse among the wound. After several minutes the platelet plug is completely formed by fibrin (Andrew et al., 2013).

Haemostasis is maintained in the body via three mechanisms:

1. **Vascular spasm (Vasoconstriction) -** Vasoconstriction is produced by vascular smooth muscle cells, and is the blood vessel's first response to injury. The smooth muscle cells are controlled by vascular endothelium, which releases intravascular signals to control the contracting properties. When a blood vessel is damaged, there is an immediate reflex, initiated by local sympathetic pain receptors, which helps promote vasoconstriction. The damaged vessels will constrict (vasoconstrict) which reduces the amount of blood flow through the area and limits the amount of blood loss. Collagen is exposed at the site of injury, the collagen promotes platelets to adhere to the injury site. Platelets release cytoplasmic granules which contain serotonin, ADP and thromboxane A2, all of which increase the effect of vasoconstriction. The spasm response becomes more effective as the amount of damage is increased. Vascular spasm is much more effective in smaller blood vessels (Panova-Noeva et al., 2019).

2. **Primary haemostasis-** Platelets adhere to damaged endothelium to form a platelet plug (Platelet plug formation) and then degranulate. This process is regulated through thromboregulation. Plug formation is activated by a glycoprotein called Von Willebrand factor(vWF), which is found in plasma. Platelets play one of major roles in the haemostatic process. When platelets come across the injured endothelium cells, they change shape, release granules and ultimately become 'sticky'. Platelets express certain receptors, some of which are used for the adhesion of platelets to collagen. When platelets are activated, they express glycoprotein receptors that interact with other platelets, producing aggregation and adhesion. Platelets release cytoplasmic granules such as adenosine diphosphate(ADP), serotoninand thromboxane A2. Adenosine diphosphate (ADP) attracts more platelets to the affected area, serotonin is a vasoconstrictor and thromboxane A2 assists in platelet aggregation, vasoconstriction and degranulation. As more chemicals are released more platelets stick and release their chemicals; creating a platelet plug and continuing the process in a positive feedback loop. Platelets alone are responsible for stopping the bleeding of unnoticed wear and tear of our skin on a daily basis. This is referred to as primary hemostasis (Andrew et al., 2013).
3. **Secondary Haemostasis -** Once the platelet plug has been formed by the platelets, the clotting factors (a dozen proteins that travel along the blood plasma in an inactive state) are activated in a sequence of events known as 'coagulation cascade' which leads to the formation of Fibrin from inactive fibrinogen plasma protein. Thus, a Fibrin mesh is produced all around the platelet plug to hold it in place; this step is called "Clot formation". During this process some red and white blood cells are trapped in the mesh which causes the primary haemostasis plug to become harder: the resultant plug is called as 'thrombus' or 'Clot'. Therefore, 'blood clot' contains secondary haemostasis plug with blood cells trapped in it. Though this is often a good step for wound healing, it has the ability to cause severe health problems if the thrombus becomes detached from the vessel wall and travels through the circulatory system; if it reaches the brain, heart or lungs it could lead to stroke, heart attack, or pulmonary embolism respectively. However, without this process the healing of a wound would not be possible (Luyendyk et al., 2019),

Coagulation

Coagulation is the process by which blood changes from a liquid to a gel, forming a blood clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion and aggregation of platelets, as well as deposition and maturation of fibrin (Long et al., 2015).

Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining the blood vessel. Exposure of blood to the subendothelial space initiates two processes: changes in platelets, and the exposure of subendothelial tissue factor to plasma factor VII, which ultimately leads to cross-linked fibrin formation. Platelets immediately form a plug at the site of injury; this is called primary haemostasis. Secondary haemostasis occurs simultaneously: additional coagulation (clotting) factors beyond factor VII (listed below) respond in a cascade to form fibrin strands, which strengthen the platelet plug (Lassila et al., 2012).

Mechanism

The mechanism by which coagulation allows for haemostasis is a complex process that is done through a series of clotting factors. The intrinsic pathway consists of factors I, II, IX, X, XI, and XII. Respectively, each one is named, fibrinogen, Prothrombin, Christmas factor, Stuart-Prower factor,plasma thromboplastin, and Hageman factor. The extrinsic pathway consists of factors I, II, VII, and X. Factor VII is called stable factor. The common pathway consists of factors I, II, V, VIII, X. factor V and VII called labile factor and Antihemophillic factor respectively The factors circulate through the bloodstream as zymogens and are activated into serine proteases. These serine proteases act as a catalyst to cleave the next zymogen into more serine proteases and ultimately activate fibrinogen. The following are serine proteases: factors II, VII, IX, X, XI and XII. These are not serine proteases: factors V, VIII, XIII. The intrinsic pathway is activated through exposed endothelial collagen, and the extrinsic pathway is activated through tissue factor released by endothelial cells after external damage (Grover et al., 2019).

Platelet Activation

Panova-Noeva et al. (2019). Reported that when the endothelium is damaged, the normally isolated, underlying collagen is exposed to circulating platelets, which bind directly to collagen with collagen-specific glycoprotein Ia/IIa surface receptors. This adhesion is strengthened further by von Willebrand factor (vWF), which is released from the endothelium and from platelets; vWF forms additional links between the platelets' glycoprotein Ib/IX/V and A1 domain. This localization of platelets to the extracellular matrix promotes collagen interaction with platelet

glycoprotein VI. Binding of collagen to glycoprotein VI triggers a signaling cascade that results in activation of platelet integrins. Activated integrins mediate tight binding of platelets to the extracellular matrix. This process adheres platelets to the site of injury (Machlus et al., 2013).

Machlus et al.(2013) also reported that activated platelets release the contents of stored granules into the blood plasma. The granules include ADP, serotonin, platelet-activating factor (PAF), vWF, platelet factor 4, and thromboxane A_2 (TXA_2), which, in turn, activate additional platelets. The granules' contents activate a G_q-linked protein receptor cascade, resulting in increased calcium concentration in the platelets' cytosol. The calcium activates protein kinase C, which, in turn, activates phospholipase A_2 (PLA_2). PLA_2 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 hemostasis) (Machlus et al., 2013).

Coagulation Cascade

The coagulation cascade of secondary haemostasis has two initial 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), which both lead to the same fundamental reactions that produce fibrin. It was previously thought that the two pathways of coagulation cascade were of equal importance, but it is now known that the primary pathway for the initiation of blood coagulation is the tissue factor (extrinsic) pathway (Meybohm et al., 2013). 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 factors are generally indicated by Roman numerals, with a lowercase a appended to indicate an active form (Madala et al., 2010).

The coagulation factors are generally serine proteases (enzymes), which act by cleaving downstream proteins. The exceptions are tissue factor, FV, FVIII, FXIII. Tissue factor, FV and FVIII are glycoproteins, and Factor XIII is a transglutaminase. The coagulation factors circulate as inactive zymogens. The coagulation cascade is therefore classically divided into three pathways. The tissue factor and contact activation pathways both activate the "final common pathway" of factor X, thrombin and fibrin (Suman et al., 2018).

Intrinsic Pathway

This pathway is the longer pathway of secondary hemostasis. It begins with the activation of Factor XII (a zymogen, inactivated serine protease) which becomes Factor XIIA (activated serine protease) after exposure to endothelial collagen. Endothelial collagen is only exposed when endothelial damage occurs. Factor XIIA acts as a catalyst to activate factor XI to Factor XIA. Factor XIA then goes on to activate factor IX to factor IXA. Factor IXA goes on to serve as a catalyst for turning factor X into factor Xa. This is known as a cascade. When each factor is activated, it goes on to activate many more factors in the next steps. As you move further down the cascade, the concentration of that factor increases in the blood. For example, the concentration of factor IX is more than that of factor XI. When factor II is activated by either intrinsic or extrinsic pathway, it can reinforce the intrinsic pathway by giving positive feedback to factors V, VII, VIII, XI, XIII. This makes factor XII less critical; patients can actually clot well without factor XII. The intrinsic pathway is clinically measured as the partial thromboplastin time with kaolin (PTTK) (Grover et al., 2019).

Extrinsic Pathway

The extrinsic pathway is the shorter pathway of secondary hemostasis. Once the damage to the vessel is done, the endothelial cells release tissue factor which goes on to activate factor VII to factor VIIa. Factor VIIa goes on to activate factor X into factor Xa. This is the point where both extrinsic and intrinsic pathways become one. The extrinsic pathway is clinically measured as the prothrombin time (PT) (Eriksson et al., 2014).

Common Pathway

This pathway begins at factor X which is activated to factor Xa. The process of activating factor Xa is a complicated reaction. Tenase is the complex that cleaves factor X into factor Xa. Tenase has two forms: extrinsic, consisting of factor VII, factor III (tissue factor) and Ca2+, or intrinsic, made up of cofactor factor VIII, factor IXA, a phospholipid, and Ca2+. Once activated to factor Xa, it goes on to activate factor II (prothrombin) into factor IIa (thrombin). Also, factor Xa requires factor V as a cofactor to cleave prothrombin into thrombin. Factor IIa (thrombin) goes on to activate fibrinogen into fibrin. Thrombin also goes on to activate other factors in the intrinsic

pathway (factor XI) as well as cofactors V and VIII and factor XIII. Fibrin subunits come together to form fibrin strands, and factor XIII acts on fibrin strands to form a fibrin mesh. This mesh helps to stabilize the platelet plug (Habib et al., 2019).

Organs Involve In Coagulation

One of the organs intimately involved in the coagulation process is the liver. The liver is responsible for the formation of factors I, II, V, VII, VIII, IX, X, XI, XIII, and protein C and S. Factor VII is created by the vascular endothelium (Chang et al., 2018).

Pathology to the liver can cause lack of coagulation factors and lead to hemorrhage. A decrease in coagulation factors typically means severe liver damage which occurs in HIV patients. Factor VII has the shortest half-life, leading to elevated PT first in liver disease (Sacoglu et al., 2018). INR can be greater than 6.5 (normal is about1.0-1.2). Coagulopathy in liver disease is treated with fresh frozen plasma.

Effect Of Hiv On Coagulation

HIV infection is known to cause coagulation abnormalities by various mechanism, especially during its late course. Hepatic damage is caused by virus itself or by the anti-retroviral (ART) drugs that may also contribute to coagulation defects in HIV patients (Lopezet al., 2012).Almost all of the coagulation factors are produced in the liver (fibrinogen, prothrombine, labile factor, stable factor, vonwillebrand factor, Christmas factor, Stuart power factor e.t.c. Therefore ultimately affects the intrinsic, extrinsic and common pathway.

Platelets play an important role in haemostasis, by forming the primary haemostatic plug following endothelial injury. Platelets decrease in HIV infection due to autoimmune destruction, direct infection of megakaryocytes by virus and ART causing thrombocytopenia (Idris et al., 2016). Platelets also decrease due to consumption coagulopathies occurring in Acquired Immune Deficiency Syndrome (AIDS). (Bibas et al., 2011). HIV infection has been associated with endothelial dysfunction which may result in activation and consumption of coagulation factors and ultimately coagulation defect most especially von willebrand disease.

HIV infection is associated with endothelial dysfunction and liver damage. Both endothelial dysfunction and liver damage can result in coagulation defect (Jiang et al., 2010). It is therefore expected that as HIV progresses coagulation abnormalities increases.Impairment of liver function during HIV infection by reducing coagulation factors adds to compromised coagulation state (Choiet al., 2011).

Since ART is known to induce hepatotoxicity, coagulation (especially vitamin k dependent) factors are also affected and this ultimately leads to impaired synthesis of these factors. The primary test routinely used for the assessment of coagulopathy are prothrombine time (PT), platelet count and partial thromboplastin time with kaolin (PTTK) (Lopez et al., 2012).

The human immunodeficiency virus (HIV) infection is becoming more complex. Hemostatic abnormalities occur frequently in the patient with HIV. HIV-related thrombocytopenia (Tr-HIV) is the most common hemostatic disorder with a high morbidity and affects patients from every risk group independently of age, sex, or stage of infection. Two mechanisms are responsible for the Tr-HIV: bone marrow failure and immunological disorders, namely, circulating immune complex deposited on the platelet membrane and the production of autoantibodies directed against platelet (Jansen et al., 2015).

Laboratory Diagnosis

Platelet Count –

Platelets, also called thrombocytes, are tiny fragments of cells that are essential for normal blood clotting. They are formed from very large cells called megakaryocytes in the bone marrow and are released into the blood to circulate. The platelet count is a test that determines the number of platelets in your sample of blood.Platelets are the cells that circulate within our blood and bind together when they recognize damaged blood vessels,when you get a cut, for example, the platelets bind to the site of the damaged vessel, thereby causing a blood clot. There's an evolutionary reason why they're there. It's to stop us from bleeding (Lassila, 2012).

When there is an injury to a blood vessel or tissue and bleeding begins, platelets help stop bleeding in three ways. They are:

1. Adhere to the injury site
2. Clump together (aggregate) with other platelets
3. Release chemical compounds that stimulate aggregation of other platelets

These steps result in the formation of a loose platelet plug at the site of the injury in a process called primary haemostasis. At the same time, activated platelets support the coagulation cascade (lassila, 2012).

Platelet count is a routine test carried out in the laboratory to estimate the total number of platelet in a sample, the test gives a platelet count per microliter (mcL) of blood.

The measurement is the number of platelets a person has, on average, per microliter.The ideal platelet range is 150,000 to 400,000 per mcL in most healthy people.Low platelet count is known as thrombocytopenia.

The most common disorder that affect coagulation in HIV patients is Thrombocytopenia. It affects 6-10% of HIV patient. A decrease in platelet count is normal in HIV patient although most platelet counts remain within normal limits

Prothrombine Time (PT)
The prothrombin time is the time it takes plasma to clot. It is a blood test that measures how long it takes blood to clot (Bain et al., 2012). A prothrombin time test can be used to check for bleeding problems. A PT test may also be called an INR test. INR (international normalized ratio) stands for a way of standardizing the results of prothrombin time tests, no matter the testing method. After addition of tissue factor (obtained from animals such as rabbits, or recombinant tissue factor, or from brains of autopsy patients

Prothrombin, or factor II, is one of the clotting factors made by the liver. (Bibas et al., 2011) Vitamin K is needed to make prothrombin and other clotting factors. Prothrombin time is an important test because it checks to see if five different blood clotting factors (factors I, II, V, VII, and X) are present therefore measures the quality of the extrinsic pathway (as well as the common pathway) of coagulation. In prothrombine time test, complete activation is indicated when activated thrombine converts fibrinogen to fibrin and extensive or localised clot are detected mechanically or optically. PT is also to check whether medicine to prevent blood clotting is working. Some nutritional deficiencies or liver disease will decrease factors prolonging PT.

Furthermore, PT and PTTK may be artificially prolonged due to the presence of an antiphospholipid antibody(APLA). Such as lupus anticoagulant, patients with APLA are prothrombotic.

A sodium citrated bottle is used, the blood sample from patient is spun at 12000rpm for 15minute. 1 in 10 that is 0.5mls of sodium citrate and 4.5ml of blood

Partial Thromboplastin Time With Kaolin (PTTK)
The partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT) is a blood test that characterizes coagulation of the blood. A historical name for this measure is the kaolin-cephalin clotting time (KCCT), reflecting kaolinand cephalin as materials historically used in the test as surface activator. Apart from detecting abnormalities, blood clotting, partial thromboplastin time is also used to monitor the treatment effect of heparin, a widely prescribed drug that reduces blood's tendency to clot (Bain et al., 2012).

Partial thromboplastin time (PTT) measures the overall speed at which blood clots by means of two consecutive series of biochemical reactions known as the intrinsic pathway and common pathway of coagulation. PTT measures the following coagulation factors: I (fibrinogen), II (prothrombin), V (proaccelerin), VIII (anti-hemophilic factor), IX (Christmas factor), X (Stuart–Prower factor), XI (plasma thromboplastin antecedent), and XII (Hageman factor).

The partial thromboplastin time test provides a convenient and sensitive screening procedure for deficiencies of thromboplastic factors, especially factors VIII and IX. The test is carried out after preincubating the plasma for 10 minutes with kaolin, and Inosithin is used as a platelet substitute. A patient's partial thromboplastin time should be regarded as abnormal if it is more than six seconds longer than the control time. In the diagnosis of haemophilia, patients' plasmas with concentrations of factor VIII as low as about 20% might be regarded as being within the range of normal, if the selected control subject's factor VIII happened to lie near the lower end of the normal

range.When mild haemophilia is suspected, discrimination may be improved by diluting both the patient's and the control plasmas 1 in 20 in haemophilic plasma. With the test modified in this way the clotting time is prolonged, though the range of differences among normal subjects is unaltered, and plasmas with factor VIII concentrations below about 30%, i.e., in undiluted plasma, would be unlikely to be regarded as normal (Erikkson et al., 2014).

The partial thromboplastin time may be similarly modified as a screening test for factor IX deficiency.

Partial thromboplasatin time with kaolin is also prolonged in HIV patients

A sodium citrated bottle is used, the blood sample from patient is spun at 12000rpm for 15minute. 1 in 10 that is 0.5mls of sodium citrate and 4.5ml of blood

Conclusion:-

Thrombocytopenia is a common feature among HIV patients, there are few reports about this condition after the invention of ART. Most researches revealed that ART significantly decreased platelet count, PT and PTTK are also on the high side due to deficient of Von willebrand Factor (factor VIII).

References:-

1. Andew, R.K. and Berndt, M.C. (2013). Bernard-Soulier syndrome: an update Thrombocytic Hemostasis; **39**: 656.
2. Bibas, M., Biava, G, and Antinori, A. (2013). HIV-associated venous thromboembolism. Mediterranean Journal of Hematology and Infectious Diseases; 3(1):e2011030.
3. Bain et al., (2012). Dacie and Lewis Pratical Hematology.11th Edition.
4. Brenchley, J.M, Vinton, C, and Tabb, B. (2012). Differential Infection Pattern of CD4+ T cells and lymphoid tissue viral burden distinguish progressive and non-progressive lentiviral infections. Blood; **120**(20):4172-4181.
5. Chang, J.C. (2018). Hemostasis based on a novel teo path unifying theory and classification of hemostatic disorders. Blood Coagulation, Fibrinolysis; **29**(27): 573-584.
6. Chaturvedi, S., Brodsky, R.A and McCrae K.R. (2019). Complement in the Pathophysiology of the Antiphospholipid Syndrome. Front Immunology; 10:449.
7. Choi, S.Y., Kim, Y, and Kim, M.J. (2011). Haematological manifestation of Human immunodeficiency virus infection and effect of highly active antiretroviral therapy on cytopenia.Korean J hematology.**46**:253-7.
8. Chun, TW & Fauci, AS, (2012) 'HIV reservoirs: pathogenesis and obstacles to viral eradication and cure', AIDS.26(10):1261–1268.
9. Cohen, MS et al (2010). The detection of acute HIV infection. Clinical Infection of Disease. 202, S270-277.
10. COAGULATION FACTOR. Clotbase.bicnirrh.res.in. Retrieved 20 May 2018
11. D Kulpa, N Chomont (2015). HIV persistence in the setting of antiretroviral therapy. Where, when and how does HIV hide? Journal of Virus Eradication.1: 59-66.
12. Elaine, M.S. and Jerome, E.G. (2013). Wintrobes clinical hematology. 13 edition. Lippincott William and Wilkins;Acquired Immunodeficiency Syndrome.
13. Eriksson, O., Ramstrom, M., Hornaeus, K., Bergquist, J., Mokhtari, D, and Siegbahn, H, (2014). The Eph tyrosine kinase receptor EphB2 and EphA2 are novel proteolytic subtrates of tissue factor/coagulation factorVIIa. The journal of Biological Chemistry. **289** (47): 32379-91.
14. Franchi, T., Eaton, S and De Coppi, P, and Giuliani, S. (2019). The emerging role of immunothrombosis in paediatric conditions. Pediatric;86(1):19-27.
15. German Advisory Committee Blood (Arbeitskreis Blut) (2016) 'Human Immunodeficiency Virus (HIV)' Transfusion medicine and hemotherapy : offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie.43 (3): 203–222.
16. Grover, S.P, and Mackman, N, (2019). Intrinsic Pathway of Coagulation and Thrombosis. Arteriosclerosis Thrombrocytic Vascular Biology.**39**(3):331-338.
17. Harris, N.S., Winter, W.E., Ledford-Kraemer, M.R. (2011). Hemostasis: A Review & Methods of Assessment in the Clinical Laboratory. Chapter 21, 265-283. IN: Contemporary Practice in Clinical Chemistry 2nd Edition, Clarke, W.
18. Harris, N.S, Winter,W.E. (2010). The International Normalized Ratio A Tool for Monitoring Warfarin Therapy. CLN.**36** (11).

19. Habib, A., Petrucci,G, and Rocca, B. (2019). Pathophysiology of Thrombosis in Peripheral Artery Disease. Curr Vascular Pharmacology.
20. Hoffbrand, A.V, Moss, P.A.H. (2011). Essential Haematology. 6th Edition. Chapters 26 (Coagulation Disorders) and 27 (Thrombosis and Antithrombotic Therapy). Wiley-Blackwell.
21. Ifeanyichukwu, M, Ezeah, S, Onyenekwe, C, Amilo, G, Ezeuqwunne, I.P. and Ifediata, F.C., (2012). Effect of malaria, HIV infection and antiretroviral therapy on some coagulation profiles.
22. Igwe, M.C., Obeagu, E.I. and Ogbuabor, A.O.(2022). ANALYSIS OF THE FACTORS AND PREDICTORS OF ADHERENCE TO HEALTHCARE OF PEOPLE LIVING WITH HIV/AIDS IN TERTIARY HEALTH INSTITUTIONS IN ENUGU STATE. Madonna University Journal of Medicine and Health Science. 2 (3):42-57.
23. Jiang, J., Fu, W., Wang, X., Lin, P, and Chen C.(2010). hIV gp120 induces endothelial dysfunction in tumour necrosis factor- alpha – activated porcine and human endothelial cells. Cardiovascular Research. **87**(2):366-74.
24. Jansen, A.J., Peng, J., Zhao, H.G. et al., (2015). Sialidase inhibition to icrease platelet counts: A treatment option for thrombocytopenia .Am J Hematology; **90:E94**-95.
25. Kibaru, E.G., Nduati, R., Wamala, D., and Kariuki, N., (2015). Impart of highly active antiretroviral therapy on haematological indce among HIV-1 infected children at Kenyatta national hospital-kenya: retrospective study.**12**:16
26. Kroll, M.H. (2010. ThromboelastographyTheory and Practice in Measuring Hemostasis. CLN; **36**(12).
27. Lassila, R. (2012). "New insight into Von Willebrand Disease and platelet Function". Seminar in Thrombosis and Hemostasis: **38**(1):63.
28. Li, G, and De Clercq, E. (2016). HIV Genome-wide protein associations: Microbiology and Molecule Biology Reviews**. 80**(3):679-731.
29. Levi, M, and Sivapalaratnam, S, (2018). Disseminated intravascular coagulation: an update on pathogenesis and diagnosis. Expert Revision Hematology; 11(8):663-672.
30. Long, A.T., kenne, E., Jung, R., Fuchs, T.A and Renne, T,(2015). Contact system revisited: An interface between inflammation, coagulation and innate immunity". Journal of Thrombosis and hemostasis. **14**(3):427-437
31. López, M., San, R.J., Estrada,V., Vispo, E., Blanco, F, and Soriano,V, (2012). Endothelial dysfunction in HIV infection-the role of circulating endothelial cells, microparticles, endothelial progenitor cells and macrophages. AIDS Revision; 14(4):223–30
32. Luyendyk, J.P. Schoenecker, J.G. and Flick, M.J. (2019). The multifaceted role of fibrinogen in tissue injury and inflammation. Blood; 133(6):511-520.
33. Lyumkis, D., Julien, J.P., De Val, N., Cupo, A., Potter, C.S., Klasse, P.J., Burton,D.R., Sanders, R.W., Moore, J.P., Carragher,B, and Wilson, I.A. (2013). Cryo- EM structure of a fully glycosylated soluble cleaved HIV- 1 enveloped trimer. Science. 342 (6165).
34. Maatens, G., Celum, C, and Lewin, S.R. (2014). Hiv infecton: epidermiology, pathogenesis, treatment and prevention; **384:258**-71.
35. Machlus, K.R. et al., Italiano, J.E. (2013). The incredible journey; from megakaryocyte development to platelet formation.Cell Biology: 201; 784-796.
36. Madala, P.K., Tyndall, J.D., Nall, T. and Fairlie, D.P., (2010). Update 1 of: Proteases universally recognise beta strands in their active sites". Chemical review; 110(**6**): PR1-31.
37. Madekwe, C.C., Madekwe, C.C. and Obeagu, E.I (2022). Inequality of monitoring in HumanImmunodeficiency Virus, Tuberculosis and Malaria. Madonna University Journal of Medicine and Health Science. 2 (3):6-15.
38. Meybohm, P., Zacharowski, K., and Weber, C.F., Point of coagulation management in intensive care medicine. Critical Medicine; **17:218**.
39. Nogami, K, and Shima, M, (2019). New therapies using nonfactor products for patients with hemophilia and inhibitors. Blood;133(5):399-406.
40. Obeagu, E.I., Amilo, G.I., Obeagu, G.U. and Nnatuanya, I.N (2017). Human Immunodeficiency Virus infection and cardiovascular disease. Int. J. Curr. Res. Med. Sci. 3(9): 9-37.
41. Oloro, O.H., Oke, T.O. and Obeagu, E.I. (2022). EVALUATION OF COAGULATION PROFILE PATIENTS WITH PULMONARY TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS IN OWO,
42. Omoregie, R., Osakue, S.I., Ihemeje, V., Omokaro, E.U. and Ogeferet, H.O. (2009). Correlation of CD4 count with platelet count, prothrombin time and activated partial thromboplastin time among HIV patients, Benin City, Nigeria. West Indian medicine; 58(5):437.

43. Panova-Noeva, M., Eggebrecht, L., Prochaska., J.H. and Wild, P.S., (2019). Potential of Multidimensional, Large-scale Biodatabases to Elucidate Coagulation and Platelet Pathways as an Approach towards Precision Medicine in Thrombotic Disease. Hamostaseologie; **39**(2):152-163.
44. Patel, P., Borkowf, C.B., Brooks, J.T., Lasry, A., lansky, A, and Mermin, J, (2014). Estimating per-act HIV transmission risk: a systemic review. AIDS: **19:28**(10); 1509-19.
45. Phasha, M.N., Soma. P, Pretorius, E, and Phulukdaree, A. (2019). Coagulopathy in Type 2 Diabetes Mellitus: Pathological Mechanisms and the Role of Factor XIII-A Single Nucleotide Polymorphisms. Curr Diabetes; 15(6):446-455.
46. Pallister, C.J, Watson, M.S (2010). Haematology. Scion Publishing. pp. 336–347. ISBN 978-1-904842-39-2.
47. Protein Data Bank (2014) HIV Envelope Glycoprotein (accessed 7 November 2018).
48. Saracoglu, A. and Saracoglu, K.T.,(2018). Coagulunopathy during liver transplantation. J Anaesthesiol Clinical Phamacology; **34**(3):289-295.
49. Samji, H, Cescon A, Hogg R.S., Modur, S.P.,Althoff, K.N. and Buchacz, K, (2013). Increases in life expentancy among treated HIV positive individuals in the United States and Canada; **8**(12):e81355.
50. Schmaier, A.H and Lazarus, H.M. (2011). Concise guide to hematology. Chichester, West Sussex, UK: Wiley-Blackwell. p. 91. ISBN 978-1-4051-9666-6.
51. Shahzad, K., Kohli S., Al-Dabetes,M.M. and Isermann, B, (2019) Cell biology of activated protein C. Curr. Opin. Hematology;26(1):41-50.
52. Shamzah, A, et al., (2013). An unusual cause of a haemorrhagic stroke: acquired haemophilia A. Case Report.
53. Shen Y. (2004). Thrombosis and a Hypercoagulable State in HIV-Infected Patients. Clinical and Applied Thrombosis/Haemostasis. 10(3):277–80.
54. Soff, G.A. (2012). A new generation of oral direct anticoagulants". Arteriosclerosis, Thrombosis, and Vascular Biology. **32** (3): 569–74.
55. Suman, M., Ramesh, P., Anindita, B, and Prosenjit, S. (2018). Synthesis of phosphstidylserine and its steroisomer: their role in actvation of blood coagulation. ACS Medicinal Chemistry Letters: **9**(5)434-439.
56. Winter, W.E., Flax, S.D. and Harris, N.S. (2017). Coagulation Testing in the Core Laboratory. Laboratory Medicine;48(**4**):295-313.
57. Zhou, T., Geogiev, I and Wu, X. (2010). Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. Science.329:811-817.