Introduction and aim of the work

Introduction

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that leads to acquired immunodeficiency syndrome (AIDS)**.** Previous names for human immunodeficiency virus include human T-lymphotropic virus-III (HLTV-III), lymphadenopathy-associated virus (LAV), and AIDS-associated retrovirus (ARV). **(Holzammer et al., 2001).**

Two strains of HIV are known to exist: HIV-1 and HIV-2. HIV-1 is the virus that was initially discovered and termed LAV. It is more virulent, relatively easily transmitted, and is the cause of the majority of HIV infections globally. HIV-2 is less transmittable and is largely confined to the West Africa **(Reever J.D and Doms R W, 2002).**

HIV infection in humans is now pandemic. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Orgnization (WHO) estimate that AIDS has killed more than 25 million people since it was first recognized in 1981. It is estimated that about 0.6% of the world's population is infected with HIV. **(Burton et al., 2002).**

Three main transmission routes for HIV have been Identified: sexual intercourse, blood transfusion and transplacental from pregnant mother to here child. HIV-2 is transmitted much less frequently by the mother-to-child and sexual routes than HIV-1 **(Boily et al., 2009).**

Unlike some other viruses, infection with HIV does not provide immunity against additional infections, particularly in the case of more genetically distant viruses. **(Smith et al., 2005).**

The term viral tropism refers to which cell types HIV infects. HIV can infect a variety of immune cells such as $CD4^+$ T cells, macrophages and microglial cells. HIV-1 entry to macrophages and $CD4^+$ T cells is mediated

through interaction of the virion envelope glycoproteins (gp120) with the CD4 molecule on the target cells and also with chemokine co-receptors. **(Clapham PR and Mckinight A ., 2001).**

HIV differs from many viruses in that it has very high genetic variability. This diversity is a result of its fast replication cycle, with the generation of 10^9 to 10^{10} virions every day, coupled with a high mutation rate per cycle of replication and recombinogenic properties of reverse transcriptase. **(Reeves JD and Doms RW., 2002).**

A strong immune defense reduces the number of viral particles in the blood stream, marking the start of infection's clinical latency stage. Clinical latency can vary between two weeks and 20 years. During this early phase of infection, HIV is active within lymphoid organs, where large amounts of virus become trapped in the follicular dendritic cells (FDC) network. **(Burton et al., 2002).**

HIV infection often causes anemia, Which results when there are too few red blood cells because they are being destroyed, are not maturing correctly and/or are not being produced adequately in the bone marrow. **(Evans RH and Scadden DT., 2000).**

Many people with HIV also have problems with their levels of white blood cells (leukocytes), HIV can attack leukocytes. When the number of white blood cells decrease, leucopenia can develop, which makes the body more prone to infections . HIV can also seriously impair the body's ability to fight off infection. People with HIV often have problems with their levels of platelets, when the body slows its production of platelets or when platelates are destroyed at a higher-than-normal rate, a condition called thrombocytopenia occurs. People with this condition bleed and bruise easily. **(Wickramashing et al., 2000).**

Introduction and aim of the work

Cytopenia is frequently encountered in HIV infected individuals. Possible pathogenic mechanisms include the following: effect of HIV infection on hematopoitic stem and progenitor cells; drug effects; infection and malignancy. Infiltration of the bone marrow by opportunistic infections and malignancies are important causes of myelosuppresion in HIV disease. **(Levine et al., 2002).**

Introduction and aim of the work

Aim of the study:

The aim of this study is to spotlight on the impact of Human Immune Deficiency Virus (HIV) infection on various hematologic components and their pathogenesis.

Human Immune deficiency virus and AIDS

Background:

Since its discovery in the 1980s, HIV has infected every continent on the globe by crossing socioeconomic, racial, ethnic, and gender barriers, and continues to contribute to human morbidity and mortality. Advances in medicine and technology have lead to new combination medications for HIV-positive patients, early HIV testing methodologies, and potential for an HIV vaccine, and they have given researchers and clinicians a larger armamentarium with which to treat and prevent the disease. Even with these vast improvements in HIV prevention, detection, and treatment, scientists have been unsuccessful in developing its vaccine. Therefore, the search for a cure for HIV remains the marathon of the millennium. **(Halligan et al., 2009).**

Thirty-three million people are currently infected with HIV worldwide (1.1 million in the United States), 26 million people worldwide have died of AIDS . The demographics of the disease continue to change within and among country and world populations, with new United States cases growing fastest among minority women. **(Dietz et al., 2008).**

Structure and genome:

Scanning electron micrograph of HIV-1 (in green) budding from cultured lymphocyte. Multiple round bumps on cell surface represent sites of assembly and budding of virions.

Figure (1): electron micrograph of HIV-1

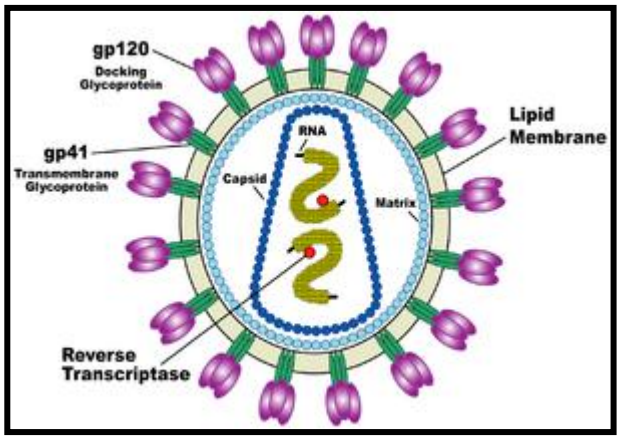

Figure (2) : Diagrame of HIV-pratical

Human immune deficiency virus in is a 120-nm retrovirus consisting of two copies of positive single-stranded RNA enclosed by a capsid of viral proteins and surrounded by a double-layered phospholipid envelope. HIV is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120 nm, around 60 times smaller than a red blood cell, yet large for a virus. **(McGovern et al., 2002).**

It is composed of two copies of positive single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24. The single-stranded RNA is tightly bound to nucleocapsid proteins, p7 and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle.This is, in turn, surrounded by the viral envelope which is composed of two layers of fatty molecules called phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and about 70 copies of a complex HIV protein that protrudes through the surface of the virus particle. (**Various, 2008).**

This protein, known as Env, consists of a cap made of three molecules called glycoprotein (gp) 120, and a stem consisting of three gp41 molecules that anchor the structure into the viral envelope. This glycoprotein complex enables the virus to attach to and fuse with target cells to initiate the infectious cycle **(Mc Govern et al., 2002).**

Both these surface proteins, especially gp120, have been considered as targets of future treatments or vaccines against HIV **(Ferrantelli et al., 2004).**

The RNA genome consists of at least seven structural landmarks (LTR,TAR, RRE, PE, SLIP, CRS, and INS) and ten genes (gag, pol, env, tat, rev, nef, vif, vpr, vpu, and tev) encoding 19 proteins. Three of these genes, gag, pol, and env, contain information needed to make the structural proteins for new virus particles. For example, env codes for a protein called gp161 that is broken down by a viral enzyme to form gp120 and gp41. The remaining genes, tat, rev, nef, vif, vpr, and vpu (or vpx in the case of HIV-2), are regulatory genes for proteins that control the ability of HIV to infect cells, produce new copies of virus (replicate) or cause disease. **(Various, 2008).**

The two Tat proteins (p16 and p14) are transcriptional transactivators for the LTR promoter acting by binding the TAR RNA element. The TAR may also be processed into microRNAs that regulate the apoptosis genes ERCC1 and IER3 **(Klase et al., 2009)**

The Rev protein (p19) is involved in shuttling RNAs from the nucleus and the cytoplasm by binding to the RRE RNA element. The Vif protein (p23) prevents the action of APOBEC3G (a cell protein which deaminates DNA: RNA hybrids and/or interferes with the Pol protein). The Vpr protein (p14) arrests cell division at G2/M. The Nef protein (p27) down-regulates CD4 (the major viral receptor), as well as the MHC class I and class II molecules. **(Stumptner-Cuvelette et al., 2001).**

Nef also interacts with SH3 domains. The Vpu protein (p16) influences the release of new virus particles from infected cells. The ends of each strand of HIV RNA contain an RNA sequence called the long terminal repeat (LTR). Regions in the LTR act as switches to control production of new viruses and can be triggered by proteins from either HIV or the host cell. The Psi element is involved in viral genome packaging and recognized by Gag and Rev Proteins. **(Various, 2008).**

History of HIV and AIDS

The history of HIV can be traced back to sub-Saharan Africa, as far back as the 1930s. (**Gilbert et al., 2007).**

In 1959, scientists isolated a virus in a human male from the Democratic Republic of Congo. They believe this virus, which was genetically similar to HIV-1 and was called SIVcpz (Chimpanzee Simian Immunodeficiency Virus), migrated from the common chimpanzee to human beings when hunters were exposed to infected ape blood. **(Lears MK and Alwood K , 2000).**

Using genetic sequencing, scientists later isolated HIV-1, group M, subtype B in a group of the earliest Haitian AIDS patients. According to their findings, this HIV clade originated in central Africa in the 1930s and arrived in Haiti in 1966, when a Haitian professional returned from working in the newly independent Congo. After circulating in Haiti, the virus diversified before migrating to the United States around 1969. It continued to diversify and cryptically circulated among United States homosexual populations until 1981, when AIDS was recognized .**(Gilbert et al., 2007).**

The 1980s and 1990s serve as the most significant historical period for HIV thus far, as this period marked the isolation and discovery of the virus that causes AIDS, the creation of guidelines to define levels of HIV infection and AIDS, and the beginning of the HIV epidemic. In 1981, the Centers for Disease Control and Prevention (CDC) reported five homosexual males in California with biopsy-confirmed *Pneumocystis carinii* pneumonia, as well as 26 cases of Kaposi's sarcoma throughout the United States. By 1982, the CDC was able to link these opportunistic infections to a new blood-borne disease, which they called “Acquired Immune Deficiency Syndrome” or AIDS **(Halligan et al., 2009).**

Multiple scientists from around the world began searching for an etiology for this disease, including Robert Gallo of the National Cancer Institute, Luc Montagnier from the Pasteur Institute in France, and Jay Levy from the University of California at San Francisco. Each of these scientists identified a retrovirus as the cause of AIDS. However, in 1983, Luc Montagnier discovered the actual virus we know today as HIV. **(Cichoki M and Montagnier L, 2004)**.

Because all three scientists had such a profound impact on the discovery of the virus, the President of the United States and the Prime Minister of France made a joint agreement in 1987 to share credit for HIV's discovery. Discovery of the virus stimulated the scientific and medical communities to not only search for a cure from HIV but also create infection-determining methodologies and epidemiologic-reporting mechanisms. **(Lears and Alwood., 2000).**

The 1990s were equally significant as the 1980s for the history of HIV. During this time period, the public became keenly aware of the virus through the efforts of Ryan White and Kimberley Bergalis. In 1990, Ryan White, a young hemophiliac patient who acquired HIV from a blood transfusion, died. However, before he died, he became an HIV/AIDS activist, gaining support from such famous personalities as Elton John and Michael Jackson, and even testifying on HIV/AIDS awareness before Congress. Then, in 1991, Kimberly Bergalis, a dental patient in Florida, made news headlines after acquiring the virus from her dentist. She, too, brought about public awareness of the disease, requesting Congress to mandate testing for all health care personnel. With awareness came increased knowledge about the sequelae of HIV infection, opportunistic infections. Therefore, by 1993, the CDC revised the definition of AIDS to include these opportunistic infections **(Halligan et al., 2009).**

Today, HIV is a leading cause of death worldwide among people ages 15 to 59. Approximately 33 million people are living with HIV/AIDS, the majority of whom reside in developing countries. These countries not only lack the infrastructure to combat HIV, but they still have cultural, financial, religious, and discriminatory barriers that prevent them from caring for their infected and affected populations. The resultant profound effects on these populations include a reduction in their economic growth and development, a stunting of their educational systems, and a decrease in their food supply. Therefore, the HIV pandemic has been described as multiple epidemics **(Halligan et al., 2009).**

The onset, prevalence, and transmission of the disease remain dynamic and vary among and within countries and world populations. For example, sub-Saharan Africa remains the region with the highest prevalence of adult and childhood HIV cases. The majority of these cases are transmitted through heterosexual contact or from mother to child . Alternatively, the HIV epidemic was first recognized in the United States as a disease with its transmission most associated with homosexual populations. However, current data suggests the primary mode of HIV transmission in the United States has changed from homosexual to heterosexual contact, with the fastest growing numbers of AIDS cases among young African American females (49%). Finally, in areas of Europe and Asia, HIV disproportionately affects intravenous drug abusers, men having sex with men, and sex workers. Because of their population growth and proximity, epidemiologists predict that countries in these regions will see the next HIV epidemic **(UNAIDS., 2008).**

AIDS: AIDS isn't a single disease, but rather a group of symptoms or illnesses that occur together. AIDS has been defined by the U.S. Centers for Disease Control and Prevention (CDC) as occurring in a person who:

- Has a laboratory-documented HIV infection.
- Has a CD4 count less than 200 cells per mL of blood .
- Has had one or more infections or types of cancer that do not occur regularly in the general population.These infections include Candida of the esophagus or lungs, disseminated tuberculosis, Pneumocystitis carinii pneumonia, several bouts of bacterial pneumonia, and extrapulmonary coccidiomycosis and histoplasmosis. The types of cancer include invasive cervical cancer, Kaposi's sarcoma, and certain types of lymphoma. People without HIV develop cervical cancer and lymphoma, but anyone known to be infected with HIV who then develops one of these conditions is considered to have AIDS **(Fan et al., 2005).**

Advanced AIDS: Anyone who has AIDS with a CD4 count less than 50 cells per mL has advanced AIDS. Survival at this stage is generally only 12 - 18 months in people not taking medications to treat AIDS. **(Wood et al., 2003).**

While the majority of people who contract HIV will ultimately develop AIDS, the time between initial HIV infection and the development of AIDS varies widely. Historically, most HIV-positive people develop AIDS within 10 to 11 years after infection; however, some people have lived with HIV for 15 years or more without symptoms. There currently is no cure for AIDS, though scientists are trying to develop a vaccine to prevent its spread. Highly active

antiretroviral therapy (HAART), has greatly prolonged the life expectancy of people living with AIDS who have access to this treatment**. (Smithet al., 2005).**

Definition and classification

Human immune deficiency virus is derived from the Retroviridae family of viruses and is a member of the genus, Lentivirus. Two species of this retrovirus infect human beings: HIV-1 and HIV-2. These viruses are the etiology of AIDS. HIV-1 originated from the common chimpanzee, is more virulent than HIV-2, and is responsible for the majority of global HIV infections. HIV-2 originated from the Sooty Mangabay, is less virulent, and is mostly confined to West Africa. HIV-1 can be subdivided into three main groups: M (90% of HIV-1 infections), N (a rare group discovered in Cameroon in 1998), and O (a group restricted to West-central Africa). Group M may be further divided into nine subtypes, called clades: A, B, C, D, F, G, H, J, and K **.(Walker BD and Burton DR , 2008).** HIV, group M, subtype B is the most widespread HIV variant **(Gilbert et al., 2007).**

Table (1): Comparison of HIV species

Species	Virulence	Transmittability	Prevalence	Purported origin
HIV-1	High	High	Global	Common Chimpanzee
HIV-2	Lower	Low	West Africa	Sooty Mangabey

(Walker and Burton., 2008).

Individuals infected with the HIV virus are called "HIV-positive" and are classified according to the centers for disease control and prevention 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults or its 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children less than 13 Years of Age. The classification system for adolescents and adults categorizes individuals based on their clinical conditions associated with HIV infection (Categories A, B, C) and their $CD4^+$ T lymphocyte counts per microliter of blood (Categories 1, 2, 3). It is based on four criteria: (*i*) repeatedly reactive screening tests for HIV antibody, with the specific antibody identified by the use of supplemental tests (eg, Western blot, immunofluorescence assay); (*ii*) direct identification of the virus in host tissues by virus isolation; (*iii*) HIV antigen detection; and (*iv*) a positive result on any other highly-specific, licensed test for HIV **(Centers for Disease Control and Prevention., 2001).**

Category A patients has asymptomatic HIV infection, persistent generalized lymphadenopathy, or acute (primary) HIV infection with accompanying illness or history of acute HIV infection. Category B patients display clinical conditions that are attributed to HIV infection, indicative of a defect in cell-mediated immunity or are considered by physicians to have a clinical course that is complicated by HIV infection. Common examples of conditions in clinical Category B include, but are not limited to oropharyngeal candidiasis (thrush), fever (38.5°C), diarrhea lasting greater than 1 month, oral hairy leukoplakia, or Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome (**Smith D et al., 2005).**

Patients who fall into Category C have one of 26 AIDS indicator conditions. Examples of such conditions include, but are not limited to esophageal candidiasis, extrapulmonary cryptococcosis, HIV-related encephalopathy, Human Herpes Virus I (HHV) greater than 1 month in duration, Kaposi's sarcoma and Mycobacterium tuberculosis or Pneumocystis carinii pneumonia. The three CD4+ T-lymphocyte categories are defined as follows: Category 1 patients have T cell counts greater than or equal to500 cells/uL, Category 2 patients have T cell counts between 200 and 499 cells/uL, and Category 3 patients have T cell counts less than 200 cells/uL. Patients in clinical Category 3 are also referred to as patients with the diagnosis of AIDS. Children less than 13 years of age infected with HIV are classified according to three parameters: (*i*) infection status, (*ii*) clinical status, and (*iii*) immunologic status **(Centers for Disease Control and Prevention., 2007).**

Pathogenesis of HIV

Each HIV viral particle consists of 72 copies of a complex protein made up of glycoproteins 120 and 41 that traverse the phospholipid envelope and enable the virus to attach and fuse to target cells. The virus sustains itself through release of viral RNA and multiple viral enzymes into host $CD4^+$ T cells, macrophages, and microglial cells. Its life cycle consists of six steps: binding/fusion, reverse transcription, integration, transcription, translation, and viral assembly and maturation. During binding, glycoprotein 120 (gp 120) adheres to the $CD4^+$ T cell, macrophage, or microglial cell, causing a conformational change in the structure of gp120 **(Burton GF et al., 2002).**

While binding is crucial for viral entry, interferes with intracellular signal transduction and promotes $CD4^+$ apoptosis, this conformational change allows

interaction of gp 120 with its coreceptor, CCR5 or CXCR4, enabling fusion. Membrane fusion is dependent on coreceptor binding and is facilitated by glycoprotein 41 (gp41). Once fusion occurs, the two single strands of viral RNA within the viral capsid are released into the host cell cytoplasm, leaving the viral envelope behind **(Noble R, 2008).**

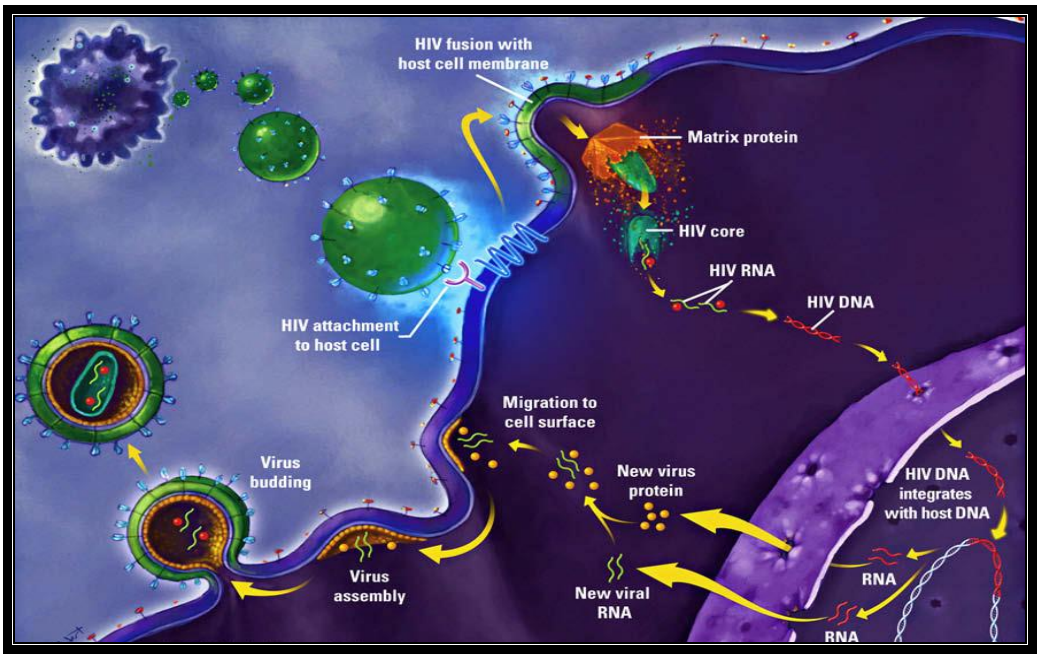

Figure (3): The HIV lifecycle **(Noble R, 2008).**

The virus then releases an enzyme, reverse transcriptase, which converts the two strands of viral RNA into double stranded DNA. The viral DNA is transported to the host cell nucleus, where it is incorporated into the host DNA through the action of the viral enzyme, integrase. Once the viral DNA is integrated, the virus is called provirus. This provirus may remain dormant for years; however, once the cell is activated, the two strands of viral DNA separate and are converted into messenger RNA (transcribed) by the host enzymes **(Arthos et al., 2008).**

The messenger RNA is then carried outside the nucleus to the mitochondria and processed. As each portion of the messenger RNA is read by

the mitochondria, a complementary set of proteins is made (translation). The proteins are cut by a viral enzyme, protease, and then used to create either new viral particles or viral enzymes. These new proteins and enzymes are then assembled and placed inside buds, which extrude from the cell. The buds of new immature viral proteins and enzymes break away from the infected host cell. Shortly after leaving the host cell, viral proteinases become active, cleaving the viral proteins to generate a mature form of HIV. Once mature, the virus is infective **(Noble R, 2008).**

Tropism

The term viral tropism refers to which cell types HIV infects. HIV can infect a variety of immune cells such as $CD4^+$ T cells, macrophages, and microglial cells. HIV-1 entry to macrophages and $CD4^+$ T cells is mediated through interaction of the virion envelope glycoproteins (gp120) with the CD4 molecule on the target cells and also with chemokine coreceptors **(Clapham PR and Mcknight A 2001).**

Macrophage (M-tropic) strains of HIV-1, or non-syncitia-inducing strains (NSI) use the β-chemokine receptor CCR5 for entry and are thus able to replicate in macrophages and $CD4^+$ T cells **(Coakley et al., 2005).**

This CCR5 coreceptor is used by almost all primary HIV-1 isolates regardless of viral genetic subtype. Indeed, macrophages play a key role in several critical aspects of HIV infection. They appear to be the first cells infected by HIV and perhaps the source of HIV production when $CD4^+$ cells become depleted in the patient. Macrophages and microglial cells are the cells infected by HIV in the central nervous system. In tonsils and adenoids of HIV-infected patients, macrophages fuse into multinucleated giant cells that produce huge amounts of virus. T-tropic isolates, or syncitia-inducing (SI) strains

replicate in primary $CD4^+$ T cells as well as in macrophages and use the α-chemokine receptor, CXCR4, for entry **(Deng et al., 1996).**

Dual-tropic HIV-1 strains are thought to be transitional strains of the HIV-1 virus and thus are able to use both CCR5 and CXCR4 as co-receptors for viral entry. The α-chemokine SDF-1, a ligand for CXCR4, suppresses replication of T-tropic HIV-1 isolates. It does this by down-regulating the expression of CXCR4 on the surface of these cells. HIV that use only the CCR5 receptor are termed R5; those that only use CXCR4 are termed X4, and those that use both, X4R5. However, the use of coreceptor alone does not explain viral tropism, as not all R5 viruses are able to use CCR5 on macrophages for a productive infection and HIV can also infect a subtype of myeloid dendritic cells, which probably constitute a reservoir that maintains infection when $CD4^+$ T cell numbers have declined to extremely low levels **(Coakley et al., 2005).**

Some people are resistant to certain strains of HIV. For example people with the CCR5-Δ32 mutation are resistant to infection with R5 virus as the mutation stops HIV from binding to this coreceptor, reducing its ability to infect target cells **(Tang and Kaslow, 2003).**

Sexual intercourse is the major mode of HIV transmission. Both X4 and R5 HIV are present in the seminal fluid which is passed from a male to his sexual partner. The virions can then infect numerous cellular targets and disseminate into the whole organism. However, a selection process leads to a predominant transmission of the R5 virus through this pathway **(Boily et al., 2009).** How this selective process works is still under investigation, but one model is that spermatozoa may selectively carry R5 HIV as they possess both CCR3 and CCR5 but not CXCR4 on their surface and that genital epithelial cells preferentially sequester X4 virus **(Berlier et al., 2005).**

In patients infected with subtype B HIV-1, there is often a co-receptor switch in late-stage disease and T-tropic variants appear that can infect a variety of T cells through CXCR4 **(Clevestig et al., 2005).**

These variants then replicate more aggressively with heightened virulence that causes rapid T cell depletion, immune system collapse, and opportunistic infections that mark the advent of AIDS **(Chohan et al., 2005).**

Thus, during the course of infection, viral adaptation to the use of CXCR4 instead of CCR5 may be a key step in the progression to AIDS. A number of studies with subtype B-infected individuals have determined that between 40 and 50% of AIDS patients can harbour viruses of the SI, and presumably the X4, phenotype **(Reeves JD and Boms RW., 2002).**

HIV-2 is much less pathogenic than HIV-1 and is restricted in its worldwide distribution. The adoption of "accessory genes" by HIV-2 and its more promiscuous pattern of coreceptor usage (including CD4-independence) may assist the virus in its adaptation to avoid innate restriction factors present in host cells. Adaptation to use normal cellular machinery to enable transmission and productive infection has also aided the establishment of HIV-2 replication in humans. A survival strategy for any infectious agent is not to kill its host but ultimately become a commensal organism. Having achieved a low pathogenicity, over time, variants more successful at transmission will be selected **(Cheney K and McKnight A, 2010).**

HIV transmission and occupational risk:

HIV is mainly found in blood, semen, vaginal fluids, and breast milk, and is transmitted through direct contact with these fluids via sexual contact, intravenous drug use, mother-to-child transfer, or occupational exposure. The

virus has also been found in small amounts in the saliva, sweat and tears of AIDS patients. Oral health care personnel, in particular, are at an increased risk for occupational exposure from a percutaneous injury because of their frequent use of needles and exposure to blood and saliva. However, no cases of HIV transmission through saliva, sweat, or tears from AIDS patients have been recorded **(Centers for Disease Control and Prevention, 2008).**

Factors that influence occupational risk include frequency of infection among patients, type of virus, and type and frequency of blood contact. Likewise, risk factors that affect transmission after a percutaneous injury include depth of the injury, amount of blood on the instrument, proximity of instrument to a vessel, and the disease status of the patient **(Halligan et al., 2009).**

Finally, virulence of the infectious organism must also be considered. Health care personnel are more likely to acquire an infection from a Hepatitis virus, such as B or C, than HIV. The CDC reports that the risk of acquiring Hepatitis C from a needle stick injury is 1.8%, while the risk of acquiring HIV from the same injury is only 0.3%. Occupational exposure to HIV through a percutaneous injury is considered a medical urgency and should be handled in a timely manner to ensure appropriate postexposure management. The CDC has developed postexposure prophylactic guidelines for health care personnel exposed to HIV-contaminated blood. These guidelines include taking a 4-week regimen of two drugs (zidovudine [ZDV] and lamivudine [3TC]; lamivudine [3TC] and stavudine [d4T]; or didanosine [ddl] and d4T) and serve to minimize the risk of seroconversion after percutaneous injury **(Centers for Disease Control and Prevention, 2008).**

Signs and symptoms:

Any particular individual's disease course may vary considerably. Infection with HIV-1 is associated with a progressive decrease of the $CD4^+$ T cell count and an increase in viral load. The stage of infection can be determined by measuring the patient's $CD4^+$ T cell count and the level of HIV in the blood **(Wood et al., 2003).**

HIV infection has basically four stages: incubation period, acute infection, latency stage and AIDS. The initial incubation period upon infection is asymptomatic and usually lasts between two and four weeks. The second stage, acute infection, which lasts an average of 28 ays and can include symptoms such as fever, lymphadenopathy , pharyngitis, rash, myalgia, malaise, and mouth and esophageal sores. The latency stage, which occurs third, shows few or no symptoms and can last anywhere from two weeks to twenty years and beyond. AIDS, the fourth and final stage of HIV infection shows as symptoms of various opportunistic infections. A study of French hospital patients found that approximately 0.5% of HIV-1 infected individuals retain high levels of CD4 T-Cells and a low or clinically undetectable viral load without anti-retroviral treatment. These individuals are classified as HIV controllers or long-term nonprogressors **(Grabar et al., 2009).**

Table (2) :Symptoms of initial infection and later disease:

Symptoms of initial infection	Symptoms of later disease
Sore throat	Enlarged lymph nodes over several areas of the body
Fever	Persistent fever, night sweats, or chills
Nausea and vomiting	Sudden unexplained weight loss
Fatigue	Persistent diarrhea
Swollen lymph nodes	Mouth sores
Headaches, muscle aches, joint pain	Persistent dry cough
Occasionally meningitis or encephalitis	Persistent oral (thrush) or vaginal yeast infections

(Grabar et al., 2009).

Rapid HIV testing

Diagnostic methodologies to detect HIV infection have improved since the discovery of the virus. Fear seems to be the main barrier for not seeking test results or treatment. Patients state this fear as fear of rejection from family and friends, job loss and loss of benefits, and fear of needles. **(Glick, 2005).**

This fear then leads to a delay in testing, continued practice of disease-transmitting behaviors, and continued progression of the disease. Because of this delay, only 40% to 50% of HIV-positive patients are diagnosed with AIDS within 1 year of first testing HIV-positive **(Samet et al., 2001)**.

The CDC recently announced an initiative to reduce barriers to early diagnosis and increase access to treatment and prevention. This initiative, "Advancing HIV Prevention: New Strategies for a Changing Epidemic," expands on the 1993 recommendations for testing inpatients and outpatients in acute-care hospital settings and stresses the importance of rapid HIV tests. **(Greenwald et al., 2006)**.

All patients who take the rapid HIV test must receive before- and after-test counseling. Before-test counseling sessions should include information about HIV/AIDS, routes of transmission, sensitivities and specificities of different tests, discrimination issues, partner notification issues, and risk-reduction behaviors. After-test counseling should include assessing the client's preparedness to receive the results, the meaning of the reactive test, and the need for confirmatory testing **(Glick, 2005)**.

Two different types of tests are used detect how far HIV infection has progressed, and to estimate the health of immune system. The first test counts the number of CD4 cells in blood, the cells of the immune system that are infected and killed by HIV. CD4 cells play a critical role in fighting off

infection and disease, and their numbers decline throughout the course of HIV infection. When CD4 count becomes very low, the risk for opportunistic infection increases. Uninfected people have a CD4 count of about 1,000. If the CD4 count is under 200, AIDS is suspected. Serious opportunistic infections can occur if your CD4 counts drops below 200.(**Wood et al., 2003**).

The second type of blood test measures the amount of HIV. This test helps determine how fast the disease will progress. It also helps the doctor determine when to begin or change the drug therapy, and can help to monitor how well a particular drug or drug combination is working. The doctor may run specific tests to determine whether the potients have or have had particular infections including tuberculosis, cytomegalovirus, and hepatitis. These tests may be blood tests, formal eye exams, or x-rays. **(Centers for Disease Control and Prevention , 2001).**

Treatment

There is currently no available vaccine or cure for HIV or AIDS **(Robb ML., 2008).** However, a vaccine that is a combination of two previously unsuccessful vaccine candidates was reported in September 2009 to have resulted in a 30% reduction in infections in a trial conducted in Thailand. Additionally, a course of antiretroviral treatment administered immediately after exposure, referred to as post-exposure prophylaxis, is believed to reduce the risk of infection if begun as quickly as possible. **(Fan et al., 2005).**

However, due to the incomplete protection provided by the vaccine and/or post-exposure prophylaxis, the avoidance of exposure to the virus is expected to remain the only reliable way to escape infection for some time yet. Current treatment for HIV infection consists of highly active antiretroviral therapy, or HAART. This has been highly beneficial to many HIV-infected individuals

since its introduction in 1996, when the protease inhibitor-based HAART initially became available. **(Schneirder et al ., 2005).**

Current HAART options are combinations consisting of at least three drugs belonging to at least two types, or "classes," of antiretroviral agents. Typically, these classes are two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI). New classes of drugs such as Entry Inhibitors provide treatment options for patients who are infected with viruses already resistant to common therapies, although they are not widely available and not typically accessible in resource-limited settings. Because AIDS progression in children is more rapid and less predictable than in adults, particularly in young infants, more aggressive treatment is recommended for children than adults. In developed countries where HAART is available, doctors assess their patients thoroughly: measuring the viral load, how fast CD4 declines, and patient readiness. They then decide when to recommend starting treatment **(Department of Health and Human Services., 2005).**

HAART neither cures the patient nor does it uniformly remove all symptoms; high levels of HIV-1, often HAART resistant, return if treatment is stopped **(Martinez-Picado et al., 2000).**

Moreover, it would take more than a lifetime for HIV infection to be cleared using HAART. **(Blankson et al., 2002).**

Despite this, many HIV-infected individuals have experienced remarkable improvements in their general health and quality of life, which has led to a large reduction in HIV-associated morbidity and mortality in the developed world.**(Chene et al., 2003).**

One study suggests the average life expectancy of an HIV infected individual is 32 years from the time of infection if treatment is started when the CD4 count is 350/µL. In the absence of HAART, progression from HIV infection to AIDS has been observed to occur at a median of between nine to ten years and the median survival time after developing AIDS is only 9.2 months. **(Morgan et al., 2002).**

However, HAART sometimes achieves far less than optimal results, in some circumstances being effective in less than fifty percent of patients. This is due to a variety of reasons such as medication intolerance/side effects, prior ineffective antiretroviral therapy and infection with a drug-resistant strain of HIV. However, non-adherence and non-persistence with antiretroviral therapy is the major reason most individuals fail to benefit from HAART. **(Becker et al., 2002).**

The reasons for non-adherence and non-persistence with HAART are varied and overlapping. Major psychosocial issues, such as poor access to medical care, inadequate social supports, psychiatric disease and drug abuse contribute to non-adherence. The complexity of these HAART regimens, whether due to pill number, dosing frequency, meal restrictions or other issues along with side effects that create intentional non-adherence also contribute to this problem. **(Heath et al., 2002).**

The side effects include lipodystrophy, dyslipidemia, insulin resistance, an increase in cardiovascular risks, and birth defects **(Saitoh et al., 2005).**

The timing for starting HIV treatment is still debated. There is no question that treatment should be started before the patient's CD4 count falls below 200, but there is some evidences that treatment should be started before the CD4 count falls below 350 **(Wang et al., 2004).**

In those countries where CD4 counts are not available, patients with WHO stage III or IV disease should be offered treatment **(WHO, 2006).**

Although the natural history of human immunodeficiency virus (HIV) infection has been altered with the use of active combination antiretroviral therapy, the chronicity of the disease and its complications continue to provide challenges to the health and care of people living with HIV infection. Hematologic complications such as anemia and other cytopenias can be seen throughout the various stages of HIV infection and occur in up to 70% of patients with acquired immunodeficiency syndrome (AIDS) **(Fan et al., 2005).**

In a study by Erhabor, the hematologic parameters of 100 antiretroviral-naive adult Nigerians with HIV/AIDS were measured. Severe anemia occurred in 80%, neutropenia in 24%, and leukopenia and thrombocytopenia in 10% of the patients. It is important to understand the risks of people with HIV infection for developing hematologic complications, as well as their sequelae and the nature and approach to their management **(Erhabor, 2005).**

Anti-retroviral drugs are expensive, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS. Research to improve current treatments includes decreasing side effects of current drugs, further simplifying drug regimens to improve adherence, and determining the best sequence of regimens to manage drug resistance**. (Ferrantelli et el., 2004)**

The ability to achieve T cell neogenesis ex vivo has been difficult except by using organ culture or, with limited success, co-culture systems. There are currently other efforts using three-dimensional matrices that permit single positive CD4 and CD8 cells to emerge from CD34+ or AC133+ bone marrow cells. While de novo T cell generation has been documented in these systems by T cell receptor excision circle analysis and a broad profile of TCR Vß chains are represented, the ability to expand this system to a clinical scale is untested. Such strategies will also require rigorous testing to assure proper T cell

selection to avoid autoimmune attack and to demonstrate that the cells may be useful in a host defense context. If successful, however, such efforts could potentially lead to the ability to generate HIV-specific immune reactivity for subsequent adoptive transfer**. (Sparano et al., 2000).**

Alternative strategies to achieve improved immune function using ex vivo T cell manipulation are also being tested. One such method involves the ex vivo expansion of existing circulating T cells in HIV individuals using a method developed by CDC that results in HIV-free population of CD4+ and CD8+ cells**. (Little et al., 2000).**

Alternative Medicine

Because HIV infection is a disease for which conventional medicine has no cure, many people with the virus seek out alternative treatments. Although some remarkable examples of success have been reported, few alternative therapies have been studied in rigorously controlled clinical trials.Acupuncture, herbal remedies, spiritual approaches, homeopathy, and non-FDA-approved drugs are sometimes used by people with HIV. Infants cannot swallow the pills that are sometimes the only available form for a given HIV medication. Very young children also have problems taking their drugs, as the drugs often taste unpleasant, or must be taken in pill form. Therefore, doctors must be vigilant when treating children with HIV. **(Coovodia H , 2004).**

HIV vaccine

Since the discovery of HIV, scientists and researchers have been unsuccessful in the search for its vaccine. Development of vaccines for diseases can take many years. For example, it took 47 years to develop the polio vaccine and 42 years to develop the measles vaccine **(Samet et al., 2001).**

Current viral vaccines induce humoral immunity (which uses antibodies to defend against free viruses), or cellular immunity (which uses activated immune cells to combat virus-infected cells). Because HIV exists as both free virus and within infected cells, the ideal vaccine would stimulate both a humoral and cellular immunity. Additionally, because approximately 80% of HIV worldwide is transmitted sexually, scientists are looking at developing a vaccine that also produces mucosal immunity **(Halligan et al., 2009).**

The Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH continues to develop research programs focused on the discovery of an HIV vaccine. Additionally, NIAID supports clinical trials currently being conducted by governmental, private and military research programs. However, a recent human trial was unsuccessful. One of the most promising studies had been the STEP study by Merck and Co. This 3,000-patient study hypothesized that high-risk patients with a low immune response to Adenovirus 5 (a cold virus used as a vector to deliver the vaccine) would have a smaller chance of acquiring HIV when exposed to the virus or would have a decrease in their viral load if they became infected, compared with those patients who received the placebo **(National Institute of Allergy and Infectious Diseases, 2008).**

Unfortunately, the study was halted in December 2007, as the data suggested that the vaccine did not support either hypothesis. Additionally, the initial results suggested that those study participants with pre-existing immunity to Adenovirus 5 had an increased chance of acquiring HIV once exposed to the virus. With this information, the scientists at NIAID have decided to rethink their goals on developing an HIV vaccine, focusing more efforts on basic research and less on human trial testing **(Halligan et al., 2009).**

Unfortunately, only a vaccine is thought to be able to halt the pandemic.This is because a vaccine would cost less, thus being affordable for developing countries, and would not require daily treatment. However, after over 20 years of research, HIV-1 remains a difficult target for a vaccine **(Ferrantelli et al., 2004).**

Prognosis

Without treatment, the net median survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype, and the median survival rate after diagnosis of AIDS in resource-limited settings where treatment is not available ranges between 6 and 19 months, depending on the study **(Zwahlen and Egger, 2006; UNAIDS, WHO, 2007).**

In areas where it is widely available, the development of HAART as effective therapy for HIV infection and AIDS reduced the death rate from this disease by 80%, and raised the life expectancy for a newly diagnosed HIV-infected person to 20–50 years **(Knoll et al., 2007).**

As new 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. Most patients die from opportunistic infections or malignancies associated with the progressive failure of immune system **(Lawn SD, 2004).**

Older adults are often an invisible at-risk population for HIV infection. More than 10% of new AIDS cases in the U.S. each year occur in people over the age of 50; however, few screening or prevention programs are targeted to older adults. As a result, most older adults infected with the virus are first

diagnosed at later stages of the disease.It is important for people over the age of 50 to continue to protect themselves from HIV infection. Even though pregnancy is no longer a concern after menopause, condom use is important because it can reduce the risk of contracting the virus or other sexually transmitted diseases**. (Shelton et al ., 2001).**

Most people infected with HIV will go on to develop AIDS, but new drug treatments can slow the progression. An estimated 95% to 100% of people infected with HIV will go on to develop AIDS, but the time from infection to late-stage disease varies widely. Before the availability of effective treatments, a person with HIV had a 1% to 2% chance of developing AIDS within the first few years of infection, increasing by 5% each year thereafter. By 10 to 11 years postinfection, most people with HIV had already developed AIDS. The availability of effective drugs and drug combinations may improve this outlook**. (Fan et al., 2005)**

Prevention:

The best management of any medical urgency or emergency is prevention. Therefore, health care personnel should implement the elements of universal precautions such as hand-washing, use of personal protective equipment, care of patient equipment and environmental surfaces, and injury preventive measures when treating patients **(Noble, 2008).**

Table(3): Prevention of HIV Transmission from Mother to Child

Time of administration	**Regimen**
Before birth	Oral administration of zidovudine (AZT) to the mother twice daily, started at 14 to 34 weeks of pregnancy and continued until birth.
At birth	Intravenous administration of zidovudine to the mother, begun during labor and continued until delivery.
After birth	Oral administration of zidovudine to the newborn for the first six weeks of life, beginning at 8 to 12 hours after birth.

(Clevesting et al., 2005).

Follow-up

During the asymptomatic phase of HIV, your physician will want to see you several times a year to monitor the progression of your disease. Every 3 to 4 months, your physician will want to perform a physical exam and laboratory tests to monitor the progression of your disease. Follow-up will be more frequent when starting or changing drug therapies. Laboratory testing will generally include CD4 counts and HIV RNA viral load testing, as well as standard blood tests to determine the health of your liver, kidneys, and other organs. During symptomatic HIV disease, follow-up will depend on your particular symptoms, infections, and stage of disease**.(Mark Schoofs, 2008).**

The rate of clinical disease progression varies widely between individuals and has been shown to be affected by many factors such as host susceptibility and immune function health care and co-infections, as well as which particular strain of the virus is involved **(Morgan et al., 2002; Campbell et al., 2005).**

Worldwide HIV & AIDS Statistics

Global HIV/AIDS estimates, end of 2008

Table(4): The latest statistics of global HIV and AIDS were published by UNAIDS in November 2009, and refer to the end of 2008.

	Estimate	Range
People living with HIV/AIDS in 2008	33.4 million	31.1-35.8 million
Adults living with HIV/AIDS in 2008	31.3 million	29.2-33.7 million
Women living with HIV/AIDS in 2008	15.7 million	14.2-17.2 million
Children living with HIV/AIDS in 2008	2.1 million	1.2-2.9 million
People newly infected with HIV in 2008	2.7 million	2.4-3.0 million
Children newly infected with HIV in 2008	0.43 million	0.24-0.61 million
AIDS deaths in 2008	2.0 million	1.7-2.4 million
Child AIDS deaths in 2008	0.28 million	0.15-0.41 million

More than 25 million people have died of AIDS since 1981. Africa has over 14 million AIDS orphans. At the end of 2008, women accounted for 50% of all adults living with HIV worldwide. In developing and transitional countries, 9.5 million people are in immediate need of life-saving AIDS drugs; of these, only 4 million (42%) are receiving the drugs.

The number of people living with HIV has risen from around 8 million in 1990 to 33,4 million at end of 2008, and is still growing. Around 67% of people living with HIV are in sub-Saharan Africa.

Global trends

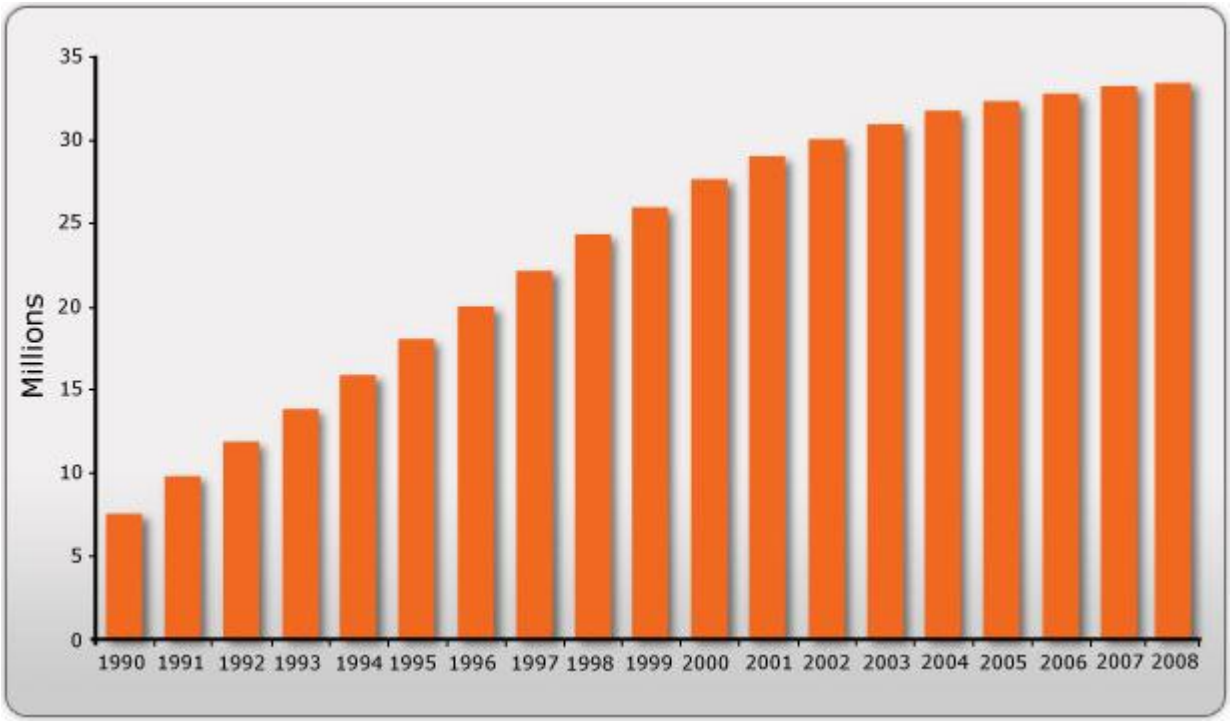

Figure (4): Proportion of adults aged 15-49 who were living with HIV/AIDS to the end of 2008

Table (5): Regional statistics for HIV & AIDS, end of 2008

Region	Adults & children living with HIV/AIDS	Adults & children newly infected	Adult prevalence	Deaths of adults & children
Sub-Saharan Africa	22.4 million	1.9 million	5.2%	1.4 million
North Africa & Middle East	310,000	35,000	0.2%	20,000
South and South-East Asia	3.8 million	280,000	0.3%	270,000
East Asia	850,000	75,000	<0.1%	59,000
Oceania	59,000	3900	0.3%	2,000
Latin America	2.0 million	170,000	0.6%	77,000
Caribbean	240,000	20,000	1.0%	12,000
Eastern Europe & Central Asia	1.5 million	110,000	0.7%	87,000
North America	1.4 million	55,000	0.4%	25,000
Western & Central Europe	850,000	30,000	0.3%	13,000
Global Total	33.4 million	2.7 million	0.8%	2.0 million

During 2008 more than two and a half million adults and children became infected with HIV (Human Immunodeficiency Virus). By the end of the year, an estimated 33.4 million people worldwide were living with HIV/AIDS. The year also saw two million deaths from AIDS, despite recent improvements in access to antiretroviral treatment.

Sub Saharan Africa HIV & AIDS Statistics

An estimated 22 million adults and children were living with HIV in sub-Saharan Africa at the end of 2007. During that year, an estimated 1.5 million Africans died from AIDS. The epidemic has left behind some 11.6 million orphaned African children. The estimated number of adults and children living with HIV/AIDS, the number of deaths from AIDS, and the number of living orphans in individual countries in sub-Saharan Africa at the end of 2007 are shown below.

Table (6): HIV & AIDS in sub-Saharan Africa at the end of 2007.

Country	People living with HIV/AIDS	Adult (15-49) rate %	Women with HIV/AIDS	Children with HIV/AIDS	AIDS deaths	Orphans due to AIDS
Angola	190,000	2.1	110,000	17,000	11,000	50,000
Benin	64,000	1.2	37,000	5,400	3,300	29,000
Botswana	300,000	23.9	170,000	15,000	11,000	95,000
Burkina Faso	130,000	1.6	61,000	10,000	9,200	100,000
Burundi	110,000	2.0	53,000	15,000	11,000	120,000
Cameroon	540,000	5.1	300,000	45,000	39,000	300,000
Central African Republic	160,000	6.3	91,000	14,000	11,000	72,000
Chad	200,000	3.5	110,000	19,000	14,000	85,000
Comoros	<200	<0.1	<100	<100	<100	<100
Congo	120,000	3.5	43,000	6,600	6,400	69,000
Côte d'Ivoire	480,000	3.9	250,000	52,000	38,000	420,000
Dem. Republic of Congo	400,000-500,000	1.2-1.5	210,000-270,000	37,000-52,000	24,000-34,000	270,000-380,000

Djibouti	16,000	3.1	8,700	1,100	1,100	5,200
Equatorial Guinea	11,000	3.4	5,900	<1,000	<1,000	4,800
Eritrea	38,000	1.3	21,000	3,100	2,600	18,000
Ethiopia	980,000	2.1	530,000	92,000	67,000	650,000
Gabon	49,000	5.9	27,000	2,300	2,300	18,000
Gambia	8,200	0.9	4,500	<1,000	<1,000	2,700
Ghana	260,000	1.9	150,000	17,000	21,000	160,000
Guinea	87,000	1.6	48,000	6,300	4,500	25,000
Guinea-Bissau	16,000	1.8	8,700	1,500	1,100	6,200
Kenya	1,500,000-2,000,000	7.1-8.5	800,000-1,100,000	130,000-180,000	85,000-130,000	990,000-1,400,000
Lesotho	270,000	23.2	150,000	12,000	18,000	110,000
Liberia	35,000	1.7	19,000	3,100	2,300	15,000
Madagascar	14,000	0.1	3,400	<500	<1,000	3,400
Malawi	930,000	11.9	490,000	91,000	68,000	560,000
Mali	100,000	1.5	56,000	9,400	5,800	44,000
Mauritania	14,000	0.8	3,900	<500	<1,000	3,000
Mauritius	13,000	1.7	3,800	<100	<1,000	<500
Mozambique	1,500,000	12.5	810,000	100,000	81,000	400,000
Namibia	200,000	15.3	110,000	14,000	5,100	66,000
Niger	60,000	0.8	17,000	3,200	4,000	25,000
Nigeria	2,600,000	3.1	1,400,000	220,000	170,000	1,200,000
Rwanda	150,000	2.8	78,000	19,000	7,800	220,000
Senegal	67,000	1.0	38,000	3,100	1,800	8,400
Sierra Leone	55,000	1.7	30,000	4,000	3,300	16,000
Somalia	24,000	0.5	6,700	<1,000	1,600	8,800
South Africa	5,700,000	18.1	3,200,000	280,000	350,000	1,400,000
Swaziland	190,000	26.1	100,000	15,000	10,000	56,000
Togo	130,000	3.3	69,000	10,000	9,100	68,000
Uganda	1,000,000	6.7	520,000	110,000	91,000	1,000,000
United Rep. Of Tanzania	940,000	5.4	480,000	130,000	77,000	1,200,000
Zambia	1,100,000	15.2	560,000	95,000	56,000	600,000
Zimbabwe	1,300,000	15.3	680,000	120,000	140,000	1,000,000
Total sub-Saharan Africa	22,000,000	5.0	12,000,000	1,800,000	1,500,000	11,600,000

(UNAIDS/WHO 2009).

Notes

Adults in this page are defined as men and women aged over 15, unless specified otherwise. Children are defined as people under the age of 15, whilst orphans are people aged under 18 who have lost one or both parents to AIDS.

HIV/AIDS in Egypt

With less than 1 percent of the population estimated to be HIV-positive, Egypt is a low-HIV-prevalence country. Unsafe behaviors among most-at-risk populations and limited condom use among the general population place Egypt at risk of a broader epidemic. According to the National AIDS Program (NAP), there were 1,155 people living with HIV/AIDS in Egypt by the end of 2007**. (National AIDS Program 2008)**

UNAIDS estimates for 2005 were higher, putting the number of HIV-positive Egyptians at 5,300. Egypt reported its first case of HIV/AIDS in 1986. Among officially reported cases, heterosexual intercourse was the primary mode of transmission (49.1 %), followed by homosexual intercourse (22.9 %), renal dialysis (12 %), and blood transfusion (6.2 %), according to the NAP in an official report issued in January 2008. Injecting drug use accounted for 2.9 percent of HIV infections and mother-to-child transmission for 1.6 %; 5.2 % are from "unknown" causes. Males are four times more likely to have HIV than females, but this may be due to more men being tested than women. Other people likely to be exposed to HIV in Egypt include street children, prisoners, and refugees. **(National AIDS Program 2008)**

Results of the United States Agency for International Development (USAID) funded Biological-Behavioral Surveillance Survey, conducted by the Ministry of Health and Population (MOHP), were disseminated in December

2006. The survey targeted street children, female sex workers (FSWs), men who have sex with men (MSM), and injecting drug users (IDUs) and identified a concentrated epidemic among MSM in Alexandria, with a seroprevalence of 6.2 %. Egypt still faces several challenges in maintaining low prevalence of HIV/AIDS. There is a general reluctance on the part of the government and civil society to discuss issues related to marginalized groups such as MSM, FSWs, and IDUs. Egypt also receives millions of tourists and refugees from countries with high HIV prevalence and/or illicit drug use rates. In addition, there are pervasive fears and stigmatization of HIV/AIDS and a lack of effective STI/HIV/AIDS education programs and other preventive measures, such as peer education and outreach and behavior change communications among at-risk groups **(Ministry of health and population 2007)**

With an estimated tuberculosis (TB) incidence of 11 new cases per 100,000 people, Egypt has relatively low levels of TB according to 2005 data from the World Health Organization. Currently, less than 1 % of adult TB patients are HIV-positive. However, continued monitoring is necessary because an increase in the incidence of HIV-TB co-infection could add to the complexity of fighting both diseases in Egypt NAP, established within the MOHP in 1986, is the official governmental body responsible for HIV/AIDS prevention**. (World health organization 2005)**

The National Strategic Plan (2006–2010) builds on the successes of the previous five-year plan and is designed to maintain the low prevalence of HIV/AIDS and improve health care services for those infected or affected by the disease. The Plan's objectives are:

- Strengthen HIV/AIDS surveillance;
- Build capacity for an expanded HIV/AIDS response;

- Increase HIV/AIDS awareness;
- Develop outreach and peer education programs for vulnerable groups;
- Expand voluntary counseling and testing (VCT) services; and
- Improve quality of life for HIV/AIDS-infected and -affected populations. Since 2005, the Government of Egypt has become more actively involved in the fight against HIV/AIDS. The government integrated HIV/AIDS into preparatory and secondary school curriculums; established nine mobile (VCT) centers and 14 fixed centers around the country; conducted trainings for physicians and nurses on clinical management and nursing care; and started to provide antiretroviral therapy (ART) for HIV/AIDS patients free of charge. By the end of 2006, according to UNAIDS, 22 percent of HIV-infected women and men were receiving ART**.(UNAIDS 2007)**

In 2006, Cairo was the site of a three-day, UNAIDS-supported workshop on HIV/AIDS and drug use in the region. The workshop included representatives of governments, non-governmental organizations (NGOs), and research programs from the arab countries as well as from Afghanistan, Iran, and Pakistan. The Government of Egypt worked with UNICEF to prevent HIV/AIDS among youth and worked with the United Nations Office on Drugs and Crime to address HIV/AIDS among IDUs**. (UNICEF 2007)**

As of March 2008, Egypt was negotiating a sixth-round grant with the Global Fund to Fight AIDS, Tuberculosis and Malaria to fight the spread of HIV/AIDS. Prevalence of HIV and AIDS in Egypt is low – ranging from 2,900 to 13,000 individuals 90% of Egyptian women who live with HIV were infected within marriage. National HIV/AIDS monitoring should be stressed in the Middle East and North Africa region, according to a report recently released by UNAIDS reports. The assessment which examined the 35,000 new HIV cases

and 25,000 AIDS-related deaths in the the assessment was the focus of last month's regional meeting on national HIV/AIDS coordination in Muscat, Oman. Officials from Algeria, Egypt, Iran, Jordan, Lebanon, Morocco, Oman Palestine, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, the United Arab Emirates and Yemen. **(UNAIDS 2009)**

Hematological Disorders

Like any part of the body, the blood can also be afflicted with diseases and disorders that can compromise the health. Disorders of the blood range from mild, with no symptoms, to life-threatening medical emergencies. **(Sacher R .A and Mcpherson R.A , 2000).**

Blood is made up of a variety of different cells, including red blood cells (erythrocytes), white blood cells (leukocytes), and cells that help in clotting (platelets) . HIV infection often causes anemia , a decrease in the number of circulating red blood cells.. Anemia results when there are too few red blood cells because they are being destroyed, are not maturing correctly, and/or are not being produced adequately in the bone marrow.Red blood cells carry oxygen throughout the body. If people don't have enough red blood cells, they begin to feel tired and breathless, and have difficulty concentrating. This can have a serious, negative effect on quality of life. Severe, untreated anemia may have complications such as heart failure and other organ damage. **(Bron D and Meuleman N, 2001).**

White blood cells are the backbone of the immune system. They fight infection by engulfing invading organisms or abnormal cells. There are five basic kinds of white blood cells : neutrophils , monocytes , lymphocytes,

eosinophils, and basophils. Neutrophils are the most common form of white blood cell and are responsible for fighting infection. **(Erhabor, 2005).**

Many people with HIV also have problems with their levels of white blood cells (leukocytes). Leukocytes are white blood cells that respond to and protect the body from infection. HIV can attack leukocytes. When the number of white blood cells decreases, a dangerous condition called leukopenia can develop, which makes the body more prone to infections.The specific type of white blood cells that respond directly to infection are called neutrophils. A decrease in these cells is called neutropenia, and can also seriously impair the body's ability to fight off infection. **(Branda et al., 2004).**

People with HIV often have problems with their levels of platelets, cells in the blood that help with clotting.When the body slows its production of platelets, and/or when platelets are destroyed at a higher-than-normal rate, a condition called thrombocytopenia occurs. People with this condition bleed and bruise easily.The drugs used to treat HIV may cause anemia and other blood disorders. The drugs used to treat HIV as well as the drugs used to combat other infections associated with HIV can cause anemia and other blood disorders. This is because these drugs can impair the production of leukocytes, red blood cells, and/or platelets in the bone marrow.Treatment for anemia targets the underlying problem first, and the symptoms of anemia second. **(Bain et al., 2001).**

Anemia is more common among people with advanced HIV infection, and signals a more rapid progression toward AIDS. In HIV, anemia of chronic disease (ACD) often occurs and results from the impairment of red cell production in the bone marrow. This impairment is due to the release of inhibitory substances (cytokines) and inappropriately low levels of the hormone

erythropoietin. ACD can also occur in people who have other infections associated with HIV**. (Bron et al., 2001).**

HIV infection itself seems to cause anemia. Late-stage HIV infection appears to have a negative effect on levels of erythropoietin, the hormone that drives the body to produce red blood cells. HIV infection may also have an effect on red blood cells, helping to decrease their lifespan in the blood and preventing the bone marrow from adequately replacing old and dying red blood cells. The HIV virus may infect early red blood cells in the marrow, altering their development. (**Abrahamian et al ., 2005).**

Drug therapy can cause blood complications by suppressing the bone marrow. The following are a few of the drugs known to cause anemia, leukopenia, or neutropenia in HIV-infected people:

- Zidovudine (AZT or Retrovir)
- Ganciclovir (Cytovene)
- Trimethoprim-sulfamethoxazole (Bactrim; Septra)
- Alpha-interferon (Roferon-A; Intron A)
- Flucytosine (Ancobon)
- Amphotericin B (Fungizone)
- Pyrimethamine (Daraprim; Fansidar) **(Montessori et al ., 2004).**

Infections associated with HIV or tumors in the marrow can cause anemia. In adults, the various cells that make up the blood are produced and mature in the bone marrow. Tumors or infections invading the marrow can disrupt this process by crowding out normal bone marrow cells. Furthermore, infections themselves can cause anemia without bone marrow invasion.

- Mycobacterium avium complex, which is in the same family as tuberculosis, is a rare infection except when it is associated with HIV. Infection probably happens after drinking or eating contaminated water or food. Once inside the body, the infection can spread to the blood, the organs, and the marrow.
- Histoplasmosis capsulatum and Pneumocystis carinii are both opportunistic infections. Both can invade the marrow and cause anemia.
- Cancers: Individuals with HIV are more prone to certain cancers, including Kaposi's sarcoma and non-Hodgkin's lymphoma.
- System. These cancers can spread to the marrow and disrupt blood cell production.
- Parvovirus B19 can cause acute anemia by stopping red blood cells from developing. In this condition, called pure red blood cell aplasia, red blood cell precursors decline sharply. **(Brill et al., 2000).**

As with anemia, thrombocytopenia (a decrease in the cells called platelets) and neutropenia (a decrease in white blood cells called neutrophils) are usually caused directly by HIV, by drugs, or by infection. Although anemia sometimes occurs alone, low blood counts tend to come in groups in HIV **(Gotllieb, 2004**).

Anemia and leukopenia, for example, tend to occur together; often in patients with advanced disease. Low levels of platelets (thrombocytopenia) may occur early in the course of the disease. HIV also appears capable of directly infecting the cells in the bone marrow that produce platelets. While uncommon, AIDS patients can develop platelet disorders called thrombotic microangiopathies. These occur when platelets rapidly start to clot in the body's small blood vessels. Red blood cells become trapped in the widespread clots,

and platelets are used up. The outcome is anemia and thrombocytopenia, often associated with organ damage. In AIDS patients, bleeding associated with infection or cancer of the digestive system may result in anemia. Widespread infections and tumors can invade the walls of the gastrointestinal tract, damaging blood vessels and allowing blood to escape into the digestive tract, resulting in anemia. **(Beers, 2003).**

Some people with HIV, particularly children, have nutritional problems that lead to anemia.

- The body's iron stores can be lost through bleeding, as occurs sometimes with cancer or infection.
- Folate deficiency causes anemia. Folate, a necessary nutrient, allows the body to produce and maintain new cells. Absorption of dietary folate is impaired in HIV disease.

Low levels of vitamin B12 also cause anemia. In HIV disease, diarrhea from medications or infections can prevent proper absorption of vitamin B12. . **(Piantadosi et al., 2007).**

Pre-existing medical conditions or medical conditions resulting from HIV infection may lead to anemia or leukopenia.

- Liver disease resulting from hepatitis C infection can cause enlargement of the spleen (splenomegaly). One of the roles of the spleen is to remove aging blood cells from the body. When the spleen is enlarged, this process can be accelerated, causing anemia. Splenomegaly can also cause decreases in the number of platelets in the blood.
- Kidney disease is an important cause of anemia. The kidney produces erythropoietin, a substance that helps drive production and maturation of

red blood cells. When the kidney is diseased, erythropoietin levels in the body are often diminished. **.(Buskin et al., 2004)**

Hematopoiesis

Hematopoiesis refers to the formation and development of various types of blood cells from the bone marrow stem cell. When the pluripotent stem cell divides in the bone marrow, it can either self-replicate or, under the influence of one or more hematopoietic growth factors, become committed to either the myeloid or the lymphoid lineage.The myeloid lineage includes cells responsible for mediating functions that include nonspecific host immune defense, clotting, and oxygen transport. The lymphoid lineage is active in providing specific host immunity. Increased production of a particular lineage is often in response to stresses such as bleeding and infection **(Clarke MF and Weissman IL , 2004).**

The myeloid cell includes erythrocytes, granulocytes (neutrophils, eosinophils, and basophils), platelets, and monocytes/macrophages. All the myeloid cell lineages arise from a common precursor cell: the myeloid stem cell or, as it has been termed based on in vitro assays, the CFU-GEMM (colony forming unit-granulocytes, erythrocytes, monocytes, megakaryocytes). The committed myeloid stem cell is considered to be multipotent as it is able to give rise to more than one cell lineage. **(Grulich et al., 2001).** In individuals with HIV infection, several causes contribute to hematopoietic suppression **(Koka,2004).**

Alterations in hematopoiesis

The presence of cytopenias in addition to the signature CD4+ T lymphopenia of HIV disease has long suggested that the suppressive effects of HIV on the hematopoietic compartment are far more broadly based than just a

select subset of T cells. A number of studies have assessed the bone marrow microenvironment, the cytokine milieu, and the number and the function of primitive hematopoietic elements in HIV disease. Each of these has supportive evidence suggesting it as a mechanism in suppressing normal cell production. **(Granovsky et al . ,1998).**

The potential for HIV infection of primitive hematopoietic cells themselves, directly suppressing hematopoiesis has been addressed in multiple different experimental settings. Progenitor populations such as those yielding megakaryocytes or monocytes are infectable; however, a very different picture has emerged for stem cells. An in vivo model in which human fetal stem cell containing fetal liver and thymic tissue are co-implanted and engrafted into an immunodeficient mouse (SCIDhu mouse) has been particularly informative. Using this system in conjunction with a reporter gene encoding recombinant HIV, Zack demonstrated that primitive cells are not directly infected though their function is markedly disturbed by the presence of the virus. This has been further supported by data from other laboratories evaluating the potential for adult human stem cell populations to be directly infected. Weichold and Young found that long term culture initiating cells assays (LTC-IC) were not affected by prior exposure of cells to HIV and no virus could be detected in the culture system. Dean assessed whether stem cells bore the molecular receptor and co-receptors necessary to permit HIV infection and found evidence of low level mRNA expression and surface protein production of CD4 and chemokine receptors, CXCR-4, and, to a lesser extent, CCR-5. While these receptors were functional in response to native ligands as evident by an intracellular calcium flux, they did not function as viral co-receptors. The cells themselves could sustain HIV infection and reverse transcription if an alternative (VSVg) viral envelope was used, but the wild type HIV envelopes were unable to gain entry

to the cell. The block to infection was either at receptor binding or virus fusion, and the mechanism remains undefined**. (Dean et al. , 1999) .**

While direct infection of stem cells does not occur, alterations in stem cell number and function have been documented. Indirect effects on hematopoietic cells due to infection of cells other than the stem/progenitor fraction have been documented in the SCID-hu mouse model , and perhaps most definitivelyconfirmed to be due to stromal elements by the studies of Bahner and Kohn. They documented that stromal support of long-term bone marrow culture in the presence of HIV was highly dependent upon the susceptibility of the stromal layer to HIV infection. When stroma endogenously or genetically altered to be uninfectible was used, hematopoiesis proceeded unimpaired, but HIV susceptible stroma resulted in diminished hematopoietic output by human or mouse primitive cells. How the microenvironment induces these alterations is unknown, but inhibitory cytokines have been implicated by studies such as that by Gradstein where TNF-αbinding protein reversed in vitro hematopoietic defects. The relationship of virus replication to inducing the hematopoietic defects is most readily apparent in the clinical changes seen when patients initiate potent anti-retroviral therapy. **(Levine et al., 2002).**

While cell production is reduced, the effect of HIV on the quantity of stem cells has been difficult to discern in vivo. The absence of a reliable method of quantitating primitive cell pools in humans restricts such an analysis. In an effort to address this issue, the AIDS Clinical Trials Group sequentially assessed the concentration of CD34+ cells in the circulation following G-CSF mobilization and generated an area under the curve analysis for patients at various stages of HIV infection. The results indicate an inverse relationship of mobilizable CD34+ cells with the baseline CD4+ cell count. While patients

with lower CD4+ cell counts had lower concentrations of CD34+ cells following G-CSF mobilization, the total number of harvestable CD34+ cells for transplant was sufficient for clinical use even among those with CD4+ cell counts below 200 cells/mm **(Grulich et al., 2001).**

1-Red Blood Cells Disorders

ANEMIA

Anemia is defined in men as a hematocrit less than 42% (hemoglobin < 14 g/dL) and in women as a hematocrit less than 37% (hemoglobin < 12 g/dL) **(Sacher and McPherson, 2000).**

Many classification systems for anemia exist. One useful classification system is based on erythrocyte size as determined by the mean corpuscular volume. Using this system, there are three broad classifications of anemia: normocytic anemia (red blood cells are normal in size), microcytic anemia (red blood cells are smaller than normal), and macrocytic anemia (red blood cells are larger than normal).The major causes of anemia in HIV disease are decreased red blood cell production, increased red blood cell destruction, and blood loss (**Abrahamian et al., 2004).**

The symptoms of anemia depend on the severity. Because the oxygen-carrying capacity of red blood cells is reduced, the symptoms of anemia are due to tissue hypoxia. The cardinal symptoms of anemia are dizziness, weakness, fatigue, and headache**.(Bron et al., 2001).**

Prevalence, Morbidity, and Mortality of HIV-Related Anemia

Anemia occurred in 18% of asymptomatic. HIV-infected patient, 50% who were symptomatic, and 75% who had progressed to AIDS. Despite

advances in the treatment of HIV infection, the prevalence of anemia in HIV disease has remained relatively constant. Anemia is more common among HIV-infected women than HIV-infected men. This may be due in part to the fact that, in general, anemia is more prevalent in women than men. Menses, pregnancy, and lactation are times when women are more at risk for anemia. Men are capable of storing greater amounts of iron, approximately 1000 mg of iron, whereas women are able to store only 300 to 500 mg. Anemia is an independent predictive marker for disease progression and death in HIV-infected patients **(Branda et al., 2004).**

Hemoglobin value was a strong independent prognostic marker for death. Likewise, successful treatment of anemia is associated with a reduction in the risk of HIV-related death **(Brill et al., 2000).**

A prospective multicenter study was conducted to evaluate the relationship between anemia and overall survival in 2,056 HIV-infected patient . Anemia was determined to be an independent risk factor for decreased survival in this population. The study found 47% of patients developed anemia by 3.5 years of follow-up. A multivariate analysis found that highly active anti-retroviral therapy (HAART) for a minimum of 6 months was associated with resolution of anemia; the protective effect of HAART against development of anemia was present 12 months or longer. **(Berhane et al., 2004).**

1- Anemia Due to Impaired Red Blood Cell Formation

a- Anemia of Chronic Illness

The most common type of anemia seen in HIV infection is the anemia of chronic illness. In the anemia of chronic illness, erythropoiesis is impaired and reticulocyte response is suppressed. HIV infection increases the body's

requirement to produce erythrocytes while at the same time decreasing the body's ability to produce these cells **(Abrahamian et al., 2005).**

Pathophysiology

The major cause of anemia in HIV disease is impaired erythropoiesis **(Mitsuyasu, 1999).**

Intrinsic immune mechanisms, opportunistic infections, opportunistic malignancies, medications, and malabsorption of vitamins, trace elements, and other nutrients may contribute independently or synergistically to impaired erythropoiesis. The anemia of chronic illness associated with HIV disease is typically associated with low serum erythropoietin levels **(Bron et al., 2001).**

A rise in the level of the inflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor, and interferon) marks the progression of HIV disease. Likewise, the degree of anemia worsens as the serum levels of these inflammatory cytokines rise in HIV-infected individuals. These cytokines have been shown to inhibit erythropoiesis in vitro. Tumor necrosis factor-α has been shown to inhibit erythropoiesis in vitro. Interferon-γ has been shown to suppress the formation of the erythroid colony-forming units **(Nemeth et al., 2004).**

Several opportunistic organisms have been shown to infiltrate the bone marrow and disrupt erythropoiesis. The most common infectious agents associated with HIV-related anemia include Mycobacterium avium complex, Mycobacterium tuberculosis, Histoplasma, Cryptococcus, Coccidiodes, Pneumocystis carinii, and Leishmania **(Smith et al., 2005).**

In immunosuppressed individuals, M. avium complex may produce a widely disseminated infection involving the blood, bone marrow, and other

tissues. M. avium infection has been highly implicated as a cause of HIV-related anemia. Anemia due to M. avium is usually isolated to a reduction in red blood cells. Anemia resulting from other organisms is frequently associated with pancytopenia. Another organism strongly associated with HIV-related anemia is Parvovirus B19 infection **(Smith , 2004).**

Several drugs used to combat HIV and its complications may contribute to the anemia that is seen in HIV disease. Zidovudine is a reverse transcriptase inhibitor that is most commonly associated with anemia in HIV disease. Zidovudine inhibits the development of erythrocytes, lympho-cytes, and platelets. Zidovudine is being administered at lower doses in combination with other antiretrovirals, the incidence of severe anemia has declined **(Tang J and Kaslow R.A , 2003).**

Anemia related to zidovudine therapy often subsides when the drug is withdrawn. Other reverse transcriptase inhibitors may be less myelosuppressive than zidovudine and should be considered for anemic patients. Zidovudine increases the mean corpuscular volume of red blood cells. Thus, mean corpuscular volume is often used as a measure of adherence to zidovudine therapy. Other drugs that increase the mean corpuscular volume are trimethoprim/sulfamethoxazole and dapsone **(Montessori et al., 2004).**

In the anemia of chronic illness, the red blood cells are usually normochromic (normal mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) and normocytic (normal mean corpuscular volume). However, microcytic, hypochromic red blood cells are sometimes seen in the anemia of chronic illness. Anisocytosis is frequently observed. Disruption of iron metabolism is manifested by low serum iron, total iron-binding capacity, and transferrin saturation with an elevated serum ferritin level **(Linker CA , 2001).**

Low serum erythropoietin levels are associated with HIV-related anemia. In a cohort study that included HIV-infected individuals at all stages of the illness, researchers in Greece identified antibodies to erythropoietin. Circulating autoantibodies to erythropoietin significantly predicted anemia and were significantly associated with higher erythropoietin levels **(Zarychanski et al.,. 2008).**

Treatment

The first step in the treatment of HIV-related anemia is to identify the underlying etiology of the anemia. Review the medications, especially the antiretrovirals, currently being taken. All assessment data, especially cardiovascular, respiratory, and skin data, should be considered when initiating therapy for HIV-related anemia. Therapy should be based not solely on the individual's hemoglobin level but also on the physical assessment data. Consider substituting another drug for one that is myelosuppressive. For instance, it is often possible to substitute another nucleoside analog reverse transcriptase inhibitor for zidovudine**.** Erythropoietin alfa, a recombinant, biosynthetic form of erythropoietin, is synthesized using recombinant DNA technology. Recombinant erythropoietin stimulates two progenitors of erythrocytes, the burst-forming units and the colony-forming units. The safety and efficacy of recombinant erythropoietin for treating anemia have been demonstrated. **(Zager et al., 2006).**

The initial dosage of erythropoietin alfa is 100 to 300 units/kg subcutaneously or intravenously three times per week. The maintenance dose is individually titrated to keep the hematocrit between 36% and 40%. The response to erythropoietin alfa depends on the endogenous serum erythropoietin level prior to treatment. A good response to erythropoietin is usually observed

in individuals with a serum erythropoietin less than 500 μU/mL. Little response to erythropoietin therapy is observed in individuals with a serum erythropoietin greater than 500 μU/mL **(American Hospital Formulary Service, 2001).**

Red cell transfusions are used with caution in HIV disease because blood transfusions have been shown to be immunosuppressive, to increase HIV replication, to accelerate disease progression, to decrease the survival time in HIV disease, and to transmit a number of blood-borne pathogens. Transfusions induce cellular immune activation, and this activation appears to increase HIV viral replication **(Zarychanski et al., 2008).**

b- Iron Deficiency Anemia

Several studies reportes that immunologic and virologic response of iron deficiency anemia in two cases of human immunodeficiency virus (HIV)-infected individuals. The findings of this report suggest that caution be exercised in prescribing iron supplements to HIV-infected patients. The treatment of iron deficiency anemia should be combined with antiretroviral agents in people living with HIV/AIDS to avoid adverse immunologic and virologic consequences (**Yusuf et al., 2002**).

Hemoglobin, ferritin, erythropoietin, tumor necrosis factor-α (TNF-α), neopterin, CD4+ lymphocyte count and plasma HIV load were measured in 165 HIV-infected and 39 uninfected 9-monthes old infants seen in an outpatient pediatric clinic in Kampala, Uganda. Among HIV -infected and uninfected infants, the prevalence of anemia (hemoglobin < 110 g/L) was 90.9 and 76.9%, respectively (P = 0.015), and the prevalence of iron deficiency anemia (hemoglobin < 110 g/L and ferritin < 12 μg/L) was 44.3 and 45.4%, respectively (P = 0.92). The relatively higher prevalence of anemia among HIV-infected infants was attributed to the anemia of chronic disease. Among

infants with and without iron deficiency, the fitted regression line was log10 plasma erythropoietin = 2.86, and log10 plasma erythropoietin = 4.11, respectively, with a difference in the slope of the regression lines between log10 erythropoietin and hemoglobin among infants with and without iron deficiency (P = 0.049). The erythropoietin response to anemia appears to be upregulated among infants with iron deficiency. The prevalence of iron-deficiency anemia appears to be extremely high among injection drug users who have human immunodeficiency virus (HIV) and/or hepatitis C (HCV) infections. Iron deficiency and its associated anemia may contribute to reduced energetic efficiency, lower aerobic capacity, decreased endurance, and fatigue. In practical terms, the functional limitations of iron deficiency and iron-deficiency anemia may affect the ability of patient to participate in work, school, social, and family activities. Iron deficiency may contribute to the cycle of poverty by limiting the ability of patient to work, earn money, and afford iron-rich sources of food. Although iron supplementation may prevent or treat iron deficiency, the use of iron supplements needs to be approached with caution in patient with HIV and HCV infections. **(Teferri A , 2001)**

Pathophysiology

Worldwide, iron deficiency is the most common type of anemia. Deficient intake of iron, malabsorption of iron, increased requirement of iron, and blood loss most commonly cause iron deficiency. Although deficient iron intake is uncommon in adults, it should be considered as a cause of iron deficiency for all HIV-infected infants, children, adolescents, and adults. Malabsorption may result from inflammatory changes of the gastrointestinal mucosa. Acute and chronic blood loss can result from conditions such as Kaposi's sarcoma, excessive menstruation, or gastrointestinal bleeding. Increased demands for iron are experienced during infancy, adolescence, pregnancy, and lactation **(Nemeth et al., 2004).**

In the United States, the average diet provides approximately 10 to 15mgof iron per day. Normally, 1 mg of iron is absorbed primarily across the mucosal cells of the duodenum and upper jejunum. Iron is transported in the blood by transferrin. In the blood, iron combines with apoferritin, a protein present in the blood, and becomes ferritin, the storage form of iron. Likewise, 1 mg of iron is lost per day through fecal or urinary excretion. Women who experience menorrhagia may lose as much as 3 to 4mg of iron per day. **(Sacher and McPherson, 2000) .**

In iron deficiency anemia, pica is frequently experienced, but the patient often fails to report unusual cravings for ice, starch, clay, or other substances. Signs of severe iron deficiency anemia include glossitis , cheilitis (fissures in the corner of the mouth), koilonychia (thin concave nails with raised edges sometimes called spoon nails), blue sclera, (**Sacher and McPherson, 2000).**

In early iron deficiency anemia, a decrease in serum ferritin may be observed. As iron deficiency anemia progresses, the red blood cells become hypochromic (decreased mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) and microcytic (decreased mean corpuscular volume). The red blood cell count may be normal during early iron deficiency. As iron stores deplete, serum transferrin usually increases. Typically, the amount of transferrin saturated with iron (transferrin saturation) decreases to less than 10%. **(Teferri A , 2001).**

Treatment

Iron supplementation can be administered orally or parenterally. The oral route is preferred because parenteral iron supplementation is associated with increased risk of anaphylaxis. Ferrous sulfate is often the oral iron preparation of choice because this form of iron is less expensive and more readily absorbed.

Ferrous gluconate and ferrous fumarate are other common iron preparations that may be administered orally. Oral administration of iron may produce constipation, diarrhea, dark stools, and/or epigastric pain **(American Hospital Formulary Service, 2001).**

Parenteral iron therapy using iron dextran should only be used when the patient is unable to tolerate any oral iron preparation or when malabsorption is the etiology of iron deficiency. Iron dextran can be given intramuscularly or as an intravenous infusion over 4 to 6 hours. Severe anaphylactic reactions have been observed following parenteral iron therapy. Anaphylactic reactions most often occur within minutes of onset of administration. Anaphylaxis is characterized by respiratory difficulty (wheezing, bronchospasm, rigor, dyspnea, and cyanosis), tachycardia, and hypotension. Because respiratory and/or cardiac arrest are possible, parenteral iron therapy should only be administered by persons who are able to deliver resuscitative measures, if needed **(American Hospital Formulary Service., 2001).**

Reticulocytosis indicates that iron supplementation is effective. Reticulocytosis should appear within 10 days following the initiation of therapy. Following the appearance of reticulocytosis, the hemoglobin is expected to rise 0.1 to 0.2 g per deciliter if iron deficiency is the etiology of the anemia **(Sacher and McPherson, 2000).**

c- Vitamin B12 Deficiency Anemia

Pathophysiology

Malabsorption is found in early stages of HIV infection and independant of secondary infections. Abnormally reduced concentrations of protein or albumin were found in 19% each, of folic acid in 41%, of vitamin B12 in 15%, of calcium in 76%, and of zinc in 28% of investigated patients. 14 patients

(47%) had an abnormal result of the H2-exhalation test, these had significantly lower serum concentrations of folic acid compared with patients who had normal test results. 13 patients (72%) had an abnormal Schilling test. 4 patients (25%) had xylose malabsorption. The frequency of abnormal serum concentrations or test results did not correlate with the stage of the disease, the presence of secondary intestinal infections, or the presence of diarrhea or weight loss. These findings demonstrate the presence of malabsorption in HIV-infected patients even at early stages of the disease, and independant of secondary intestinal infections. This argues strongly for HIV itself as causative factor. Malabsorption could cause gastrointestinal symptoms in HIV infected patients but is also found in the absence of diarrhea or weight loss. Nutrient deficiences may contribute to neurological (vitamin B12), hematological (vitamin B12, folic acid), and immunological morbidity in HIV infection. The higher frequency of vitamin B12- and lactose-malabsorption compared with xylose-malabsorption indicates a preferential impairment of specific mechanisms of absorption in HIV infected patients**. (Zeitz et al., 1991).**

Vitamin B12 is required for folate metabolism. Therefore, vitamin B12 deficiency also leads to defective DNA synthesis. There are two forms of vitamin B12, cyanocobalamin and hydroxycobalamin, which are synthesized by microorganisms ubiquitous in nature. Humans obtain vitamin B12 from eating meat. The average American diet provides 5 to 30 μg of vitamin B12; however, only 1 to 5 μg are absorbed. The liver stores from 3000 to 5000 μg of vitamin B12, enough to meet the requirements for about 6 months. For that reason, dietary deficiency of vitamin B12 is rarely ever the cause of vitamin B12 deficiency in this country **(Sacher and McPherson, 2000).**

Inflammatory changes to the ileal wall secondary to HIV disease may lead to decreased absorption of B12. Because intestinal bacteria use the vitamin

B12 present in the intestinal lumen, another cause of vitamin B12 deficiency is bacterial overgrowth. Bacterial overgrowth often follows aggressive antibiotic therapy and may increase the amount of vitamin B12 that is used **(Phillips and Groer., 2002).**

In addition to the general symptoms of anemia, the person with vitamin B12 deficiency may present with gastrointestinal symptoms such as a sore mouth, a beefy or atrophic tongue (glossitis), or diarrhea. In addition, neurologic signs due to peripheral neuropathy (i.e., impaired gait, paresthesia, and decreased vibratory sense in the extremities) may be seen. Neurologic signs may also include decreased ability to think and personality change **(Sacher and McPherson, 2000).**

Treatment

Cyanocobalamin (vitamin B12): Although cyanocobalamin may be given orally in large doses, it is poorly absorbed from the gastrointestinal tract in the absence of intrinsic factor. Cyanocobalamin may also be given nasally. The preferred route is subcutaneously or intramuscularly. For pernicious anemia, lifelong vitamin B12 therapy is required **(Sacher and McPherson, 2000).**

d- Folate Deficiency Anemia

Patients of the two groups (41 in TMP/SMX group, 36 in pentamidine group) were comparable for clinical features, initial CD4 count, zidovudine treatment and follow-up duration (3-26 months, mean 13). In group receiving TMP/SMX, severe folate deficiency (serum folate < 4 nmol/ml and/or erythrocyte folate < 300 nmol/ml) was observed in 15% (6 cases, all with wasting syndrome). Severe folate deficiency was not observed in pentamidine group ($p < 0.05$). These findings suggest that folinic acid should not be

systematically added to prophylactic regimens using cotrimoxazole, except for patients with wasting syndrome**.(Reynes et al., 1993).**

Pathophysiology

Folic acid is necessary for thymidine synthesis: Thymidine is an amino acid that is found in DNA but is absent in RNA. Thus, folate deficiency impairs the synthesis of DNA in the developing red blood cells. The most likely cause of folic acid deficiency anemia in the general population is inadequate dietary intake. A number of drugs that are used in the treatment of HIV disease antagonize the use of folate. These include trimethoprim, methotrexate, and trimetrexate. A drug that decreases the absorption of folic acid is the antitubercular drug cycloserine. Giardial infestation may impair the absorption of folic acid. **(Sacher and McPherson, 2000).**

The signs and symptoms of folic acid deficiency anemia are the same as for vitamin B12 deficiency anemia. Neurological signs and symptoms may not be present **(Teferri, 2001).**

Folate deficiency anemia is manifested by a low serum folic acid level (< 3 ng/mL) and a low red blood cell folic acid level (< 165 ng/mL). An effective response to folic acid therapy is indicated by a prompt and pronounced increase in the number of circulating reticulocytes **(Sacher and McPherson, 2000).**

Treatment

Except for cases in which malabsorption is the basis for folic acid deficiency, a daily dose of folic acid 1 to 2 mg by mouth is sufficient. In cases where folic acid deficiency is due to malabsorption, a daily parenteral dose of 1 to 2 mg folic acid may be administered **(American Hospital Formulary Service, 2001).**

2- Anemia Due to Increased Red Blood Cell Destruction

The association of acute cytomegalovirus infection with severe autoimmune hemolysis has not yet been reported in patients with HIV infection. The case is described of a 9-month-old infant with congenital HIV-1 infection who presented with severe autoimmune hemolysis and a high cytomegalovirus viral plasma load. Alternative causes of the hemolysis, such as drugs or other infections, were ruled out. After birth and after successful therapy of hemolysis, cytomegalovirus was not detected in the plasma, strongly suggesting a causal relationship between the hemolysis and cytomegalovirus infection. Severe autoimmune hemolysis should thus be considered as a cytomegalovirus-associated complication in HIV infection. In patients with human immunodeficiency virus (HIV) infection, normochromic-normocytic anemia is common. Only four cases of autoimmune hemolytic anemia have been reported in patients with the acquired immunodeficiency syndrome (AIDS) , despite the frequent finding of a positive Coombs direct test in the absence of frank hemolysis. Describe the first case of autoimmune hemolytic anemia in a HIV-positive asymptomatic person discoverd in May 1987; a 38-year-old HIV-positive bisexual man had worsening asthenia, malaise, fatigue, and jaundice. The patient denied either intravenous drug abuse or recent therapeutic drug intake. On admission, he was pale and mildly, Puppo and colleagues reported a case of autoimmune hemolytic anemia in a human immunodeficiency virus (HIV) seropositive, asymptomatic person. Have also seen two otherwise asymptomatic patients with autoimmune hemolytic anemia have also seen in a 35-year-old white man, known to be HIV seropositive was admitted on 7 November 1988 because of weight loss, weakness, diarrhea, and vomiting. He had not been taking medication. On examination he was afebrile, normotensive, and had generalized lymphadenopathy and hepatomegaly. Laboratory values were as follows: leukocyte count, 4200 mm^3; hemoglobin,

9.1 g/dL; hematocrit, 26.6% with normochromic, normocyte indices; platelet count, 138 X 10 mm^3; reticulocyte. A young HIV-infected patient presented with a severe auto-immune haemolytic anaemia with both warm and cold auto-antibodies, an infrequent category of anti-erythrocyte auto-immunity. Serological findings were compatible with the presence of a low-titre, high-thermal-amplitude anti-cold-reacting antibody and a pan-reactive warm-reactive auto-antibody. Immunochemical characterisation of the warm antibody failed to identify any membrane protein acting as auto-antigen. This is the first reported case of mixed-type autoimmune haemolytic anaemia in a patient with HIV infection. Overt haemolysis is a very rare complication in HIV-infected patients, despite the high prevalence of a positive direct antiglobulin test reported in these patients. This suggests that HIV infection is a condition in which anti-erythrocyte auto-immunity is a serological finding without haemolytic effects in the large majority of cases. **(Angelis et al., 1995) .**

In warm AIHA, which is primarily idiopathic, autoantibodies are composed of immunoglobulin G (IgG), they bind RBCs at 37°C (normal body temperature), and they alter RBCs, changing them into spherocytes. Identified causes of warm AIHA include human immunodeficiency virus (HIV) infection. When AIHA occurs as a secondary disorder associated with another medical condition, treatment of the other condition can improve AIHA. When AIHA occurs together with autoimmune thrombocytopenic purpura, an autoimmune disorder causing low platelet counts, it's known as Evans' syndrome. Evans syndrome has been reported to occur in patients with myasthenia gravis and other autoimmune conditions, Today, the treatment for chronic hepatitis C in HIV coinfected patients is a combination of Peg-IFN alpha-2a or 2b and RBV, for a period of at least 48 weeks, independent of the HCV genotype12. In this context, severe anemia leading to drug withdrawal is uncommon. Autoimmune

drug-induced hemolytic anemia in chronic mono-HCV-infected patients has been reported, as well as autoimmune hemolytic anemia associated with HCV or HIV infection. **(Brau et al., 2005).**

In the case reports presented here, the two HIV/HCV coinfected patients developed autoimmune hemolytic anemia that was probably related to the use of Peg-IFN alpha-2a. It is worth noting that, in both cases, anemia occurred in two distinct phases. In the first phase, the Hb levels decreased during the first four weeks of treatment and stabilized at around 9g/dl. They remained at that level up to the 20th week, probably due to the action of RBV on the erythrocytes. Thereafter, the Hb levels fell abruptly to below 5g/dl over a few weeks, even after drug withdrawal. This late anemia, with laboratory results indicative of autoimmune hemolysis, was probably secondary to the immunomodulatory action of Peg-IFN1 and may have been influenced by the HIV infection.**(Moccia et al., 2007)**.

In one of the drug-induced classical hemolysis mechanisms, it is considered that the antibody recognizes the antigen complex on the erythrocyte-drug surface. In this situation, the eluate and antibody search will be negative, although the direct antiglobulin test is positive. In Case 1, however, both the eluate and antibodies were positive, probably due to concomitant and sometimes oscillating autoimmunity induced by the HIV disease. It is noteworthy that in both cases, the Hb levels increased over a short period of time (seven weeks) after discontinuation of treatment, was still positive. In addition, the observed occurrence of late anemia leads to the recommendation of frequent monitoring of Hb levels throughout the treatment, even among patients with stable hematological parameters during the first 20 weeks of therapy. **(Saif MW.,2001).**

a- Antibody-Mediated Hemolytic Anemia

Pathophysiology

Frequently, HIV-infected individuals present with hyper-gamma-globulinemia (excessive gamma globulin in the blood). A positive direct Coombs' test, indicating the attachment of immunoglobulins to the red blood cell membrane, is generally seen in non-AIDS related antibody-mediated hemolytic anemia. Although approximately 20% to 40% of HIV-infected individuals have a positive direct Coombs' test. **(Telen et al., 1990),** the incidence of AIDS-related antibody-mediated hemolytic anemia is rare. HIV-infected individuals who experience antibody-mediated hemolytic anemia become severely anemic and often require numerous transfusions Other signs of AIDS-related antibody-mediated hemolytic anemia include a low serum haptoglobin, microspherocytes on the peripheral blood smear,splenomegaly, increased indirect bilirubin, and hyperplasia of the red blood cell precursors in the bone marrow. A characteristic finding of antibody mediated hemolytic anemia is reticulocytosis; however, reticulocytosis is noticeably absent in AIDS related antibody-mediated hemolytic anemia **(Saif MH., 2001).**

Treatment

Treatment of AIDS-related antibody-mediated hemolytic anemia includes glucocorticoids, intravenous gamma-globulin, and splenectomy

b- Glucose-6-Phosphate Dehydrogenase Deficiency

Pathophysiology

Glucose-6- phosphate dehydrogenase (G6PD) is a protein required for aerobic glycolysis. In red blood cells, G6PD catalyzes the conversion of glucose to glutathione. Glutathione prevents hemoglobin from becoming denatured. In

the presence of glutathione deficiency, oxidative destruction of the globin chains of hemoglobin occurs, and the red blood cell membrane becomes damaged. Most individuals with G6PD deficiency are asymptomatic most of the time and often reach adulthood before learning that they have G6PD deficiency. Certain drugs that are used in the treatment of HIV and other conditions, such as malaria, are known to induce hemolysis is G6PD-deficient individuals. **(Sacher and McPherson, 2000).**

G6PD deficiency is one of the most prevalent genetic disorders known. G6PD deficiency is transmitted by an X-linked recessive pattern of inheritance. G6PD deficiency is expressed in men who inherit the gene from their mothers who are carriers. G6PD deficiency is expressed in women only when both X chromosomes contain the gene (homozygous). G6PD deficiency is more common in African Americans, Asians, and people of Mediterranean descent **(Sacher and McPherson, 2000).**

Addition of certain drugs may result in the formation of Heinz bodies in an in vitro blood sample. Other tests that can be used to confirm the diagnosis of G6PD deficiency are the methemoglobin reduction test (sensitive), the ascorbate-cyanide test (not specific), the fluorescent spot test (sensitive and specific), and the specific G6PD assay (sensitive and specific). **(Sim et al., 1997).**

Treatment

Prevention remains the best treatment for G6PD deficiency hemolytic anemia. Avoid oxidant drugs that may precipitate a hemolytic crisis **(Phillips and Groer, 2002).**

3- Anemia Due to Increased Blood Loss

a- Chronic Blood Loss Anemia

Pathophysiology

Chronic blood loss occurs in AIDS and contributes to the high incidence of anemia in this population. It is important to note that the anemia of HIV disease is often multifactorial, and therefore much blood loss may precipitate symptoms. Early in chronic blood loss, the red blood cell morphology is normal. As chronic blood loss continues, the red blood cells become hypochromic and microcytic, indicating an inability of the bone marrow to adequately replace the erythrocytes that are being lost through chronic bleeding. The origin of chronic bleeding is most commonly in the gastrointestinal tract. Hemorrhagic cystitis due to infection may also be the etiology of chronic bleeding **(Ghez et al., 2000).**

Within the gastrointestinal tract, cytomegalovirus (CMV) is the most common cause, although blood loss from gastrointestinal lymphoma or Kaposi's sarcoma may also contribute. When blood loss occurs very slowly, patients adapt and are often asymptomatic until the hemoglobin and hematocrit become very low. The patient with AIDS may be weakened by a number of other pathophysiological processes, however, and may become symptomatic earlier than a well person who develops chronic blood loss.**(Phillips and Groer, 2002).**

Treatment

Treatment of chronic blood loss is directed at ascertaining the etiology and appropriately treating it to achieve hemostasis, whenever possible. Transfusions may be required to return the hemoglobin and hematocrit to

normal values. Increasing dietary iron sources is usually recommended, although iron can irritate the gastric mucosa and should be used carefully in the patient with AIDS-related gastrointestinal diseases **(Phillips and Groer, 2002).**

b- Acute Blood Loss Anemia

Pathophysiology

The individual with HIV disease is at risk for both acute and chronic blood loss mainly through gastrointestinal bleeding, with upper gastrointestinal bleeding occurring more commonly than lower. Because of underlying thrombocytopenia, the risk of bleeding from any lesions increases dramatically in the person with AIDS **(Chalasani N and Wilcox C.N ., 1999).**

Upper gastrointestinal bleeding is most often associated with non-HIV-related factors, such as peptic ulcer disease and gastritis, whereas lower gastrointestinal bleeding is more commonly associated with HIV. A number of opportunistic infections can cause erosions and ulcerations of the gastrointestinal mucosa. The most prevalent infection is with CMV, which is the most common viral pathogen in patients with AIDS. CMV infection of the gastrointestinal tract causes inflammatory changes that lead to focal thrombosis, occlusion, ischemia, and mucosal ulceration **(Poles M and Dieterich D., 1996).**

The friable, damaged mucosa bleeds easily, and ulcerative lesions may even perforate through the muscularis mucosa. There are several sites of CMV infection, but the esophagus and colon are the most common. Esophageal involvement can occasionally present as upper gastrointestinal bleeding, whereas CMV colitis leads to hematochezia, diarrhea, cramping, and abdominal pain. Other causes of colitis in AIDS include Cryptosporidium, Shigella, Salmonella, Campylobacter, and Clostridium difficile. Anorectal ulcerations

and fissures are an additional, fairly common cause of bleeding in patients with AIDS and can be due to CMV, Chlamydia, Treponema, herpes simplex virus, and HIV **(Poles M and Dieterich D., 1996).**

Human immunodeficiency virus infection may be associated with bacterial and fungal lesions in other organs, which may ultimately lead to bleeding. **(Mazzoni et al., 2000).**

Massive bleeding into the peritoneum can also occur. Acute blood loss occurs during hemorrhage, usually from the gastrointestinal tract or the uterus. **(Phillips and Groer, 2002).**

Treatment

The debilitated patient with AIDS who suffers hemorrhagic blood loss will require lifesaving efforts and transfusions to recover volume and oxygen carrying capacity in most cases. The volume of blood, and the loss of cells, will be replaced over time if the patient recovers from the massive bleeding, although it may take 3 to 6 weeks for full recovery **(Phillips and Groer, 2002).**

2-Platelates And Coagulation Disorders

1-Thrombosis

Previous reports indicate that venous thrombosis is an infrequent problem in patients with HIV infection. Despite this, various HIV-related factors have been proposed as potentially thrombogenic and an HIV-related hypercoagulability has been suggested. At the present time, there exists no consensus of opinion regarding prophylaxis against venous thrombosis for hospitalized patients with HIV. Patients infected by the human immunodeficiency virus represent a model in which endothelial proliferation and/or damage are of concern. Von Willebrand factor (VWF) plasma values as

a presumed marker of endothelial proliferation in patients with the lymphadenopathy syndrome (LAS) (n = 45), AIDS-related Kaposi's sarcoma (KS) (n = 23), and AIDS opportunistic infections (n = 9), in comparison with normal controls (n = 19) and classical KS (n = 12). VWF was increased in AIDS patients with KS, in AIDS patients without KS, and to a lesser extent in classical KS and LAS patients. **(Bec ker et al., 2004).**

To evaluate the diffusion of vascular proliferation in HIV-infected patients. The number of vessels within the superficial dermis of clinically uninvolved skin by an indirect immunoperoxidase method were reported. By using an antibody directed against VWF in skin biopsies from 20 LAS patients and 10 AIDS-related KS patients compared to 11 controls and 10 classical KS patients. An increase in the number of blood vessels in normal skin was found in LAS, classical KS, and AIDS-related KS. Statistical studies and comparisons between plasma and cutaneous values of VWF indicate that plasma VWF is a good marker of endothelial damage but a poor marker of vascular proliferation in HIV-infected patients**. (Laing et al., 2000).**

Thrombosis of upper extremity arteries is most commonly due to atherosclerosis of the proximal subclavian artery, trauma, or catheter-related injury. In the absence of an identifiable cause, a search for a hypercoagulable state is indicated. Hematologic manifestations of human immunodeficiency virus (HIV) infection and AIDS are frequent occurrences. The most important of these are cytopenias (anemia, neutropenia, and thrombocytopenia). The incidence and severity of cytopenia are generally correlated to the stage of the HIV infection. In addition, various coagulation abnormalities have been reported in HIV-infected patients. Apart from thrombocytopenia, these have included a prolonged APTT due to the presence of lupus anticoagulant, an increased prevalence of protein S and heparin cofactor II deficiency, and

hypoalbuminemia-related fibrin polymerization defects. HIV infection has also been associated with endothelial dysfunction. Although for the most part asymptomatic, elevated d-dimer levels have been found in HIV-infected patients, suggesting the existence of a prethrombotic state. In fact, clinical thrombosis eventuates in 2% of these patients. Documented thrombosis have involved both veins and arteries. Patiant can devoleps an acute thrombosis of his brachial artery as the initial manifestation of HIV infection.**(Misha et al., 2000).**

The recent reports of thrombotic episodes occurring in patients with human immunodeficiency virus (HIV) infection and various abnormalities predisposing to a hypercoagulable state have also been reported in such patients. To study the incidence of thrombosis in patients infected with HIV, and to assess the correlation of thrombosis with the degree of immunosuppression as well as the association with active illnesses and neoplasms. The diagnosis of thrombosis was based on documented reports of venous plethysmography or venography for deep venous thrombosis and ventilation-perfusion scan or pulmonary angiography for pulmonary embolus. Risk factors for thrombotic disease were evaluated including general risk factors such as family history, ambulatory status, medications, and data were also collected regarding CD4 cell counts and the presence of concurrent or remote opportunistic infections, acquired immune deficiency syndrome (AIDS)-related malignancy or other AIDS-related diseases at the time of diagnosis of the thrombotic event. The difference was significant, with $p = 0.00004$, and the estimated odds of an event given CD4 cell counts less than $200/mm^3$ is 29.89 (95% confidence interval). Three patients had abnormalities of anticoagulation proteins. There was a history of opportunistic infections in 5 patients and malignancy in 3 patients. Two patients with autoimmune hemolytic

anemia (AIHA) secondary to HIV-infection developed PE upon transfusion of packed red blood cells. The results of this study suggests that AIDS appears to predispose to thrombosis. It also revealed a significant correlation between thrombotic disease and CD4 counts (<200/mm) as well as the presence of opportunistic infections, AIDS-related neoplasms, or autoimmune disorders associated with HIV such as AIHA. Therefore, clinicians caring for these patients should be aware of thromboembolic disease as a possible complication of AIDS. Further studies to elucidate the mechanisms underlying this abnormal hemostatic profile, the epidemiology, and to answer several questions such as should patients with risk factors for HIV infection who develop thromboembolic complications be further evaluated including tests for HIV are warranted**. (Muhammad et al ., 2001).**

Studies have alluded to an increased prevalence of venous thrombosis in human immunodeficiency virus positive (HIV-positive) patients. Although a relationship between HIV infection and thrombotic disease has been suggested, the mechanisms predisposing to thrombosis have not been fully elucidated **(Fultz et al., 2004).**

To determine possible coagulation factor abnormalities that could explain the predisposition to thrombosis in HIV-infected patients, with acute upper segment deep vein thrombosis (DVT) confirmed by duplex ultrasound, were enrolled. Patients who had recognisable risk factors such as recent surgery, pregnancy or malignancy, were excluded. After informed consent, blood samples were taken for baseline tests as well as a thrombophilia screen. The control group comprised known HIV-positive patients without DVT (**Saif et al., 2001).**

Patients with DVT who were found to be HIV-negative were also analysed. Analysis was done in 2 parts: HIV-positive patients with and without thrombosis and HIV-positive and negative patients with thrombosis were compared. Results Part A: HIV-positive patients with and without thrombosis Of the 77 patients with DVT, 50 patients tested HIV-positive. These 50 patients (HIV-positive DVT-arm), as well as 56 controls (HIV-positive, no DVT), were enrolled into the study. The groups were well matched with regard to age, sex and cluster designation 4 (CD4) count**. (Klein et al., 2005).**

On univariate analysis, significant findings in the DVT-arm were a history of active tuberculosis on treatment, low protein C levels and a positive qualitative D-dimer, whereas on 6 multivariate analyses, only tuberculosis and an elevated D-dimer proved to be significant. Part B: HIV-positive and negative patients with thrombosis. There were 20 HIV-negative patients with DVT were used as inclusion criteria. Limited assessment was done on this group owing to unavailability of some data.The mean age of the HIV positive DVT group was significantly lower than the HIV-negative group with DVT (31.78 vs. 41.45 years; p=0.005). There was no significant difference in the prevalence of tuberculosis between the HIV-positive and HIV-negative patients with thrombosis (p = 0.269). Mean protein C levels were reduced in the HIV-positive group and normal in the HIV-negative group. They were significantly lower in the HIV-positive patients compared to the negative group (p=0.02) . The findings of the study suggest a relationship between HIV, its complications and DVT. Although this study confirms HIV infection as a risk factor for thrombosis, clear pathogenetic mechanisms remain to be elucidated. Tuberculosis appears to be an important risk factor predisposing patients to the development of DVT, both in the HIVpositive and negative population. **.(Jacobson et al., 2004**).

Thrombotic microangiopathy (TMA) is also a well recognized complication of HIV disease, seen in 1.4% of affected patients before the introduction of HAART **(Gervasoni et al., 2002).**

The antiphospholipid antibody syndrome (APS) is a thrombophilic syndrome, defined by the presence of elevated antiphospholipid antibody (aPL). The presence of elevated aPL has been described during the course of human immunodeficiency virus (HIV) infection but has not been commonly associated with thrombosis. Four HIV- infected patients, two children and two adults, with vascular manifestations suggestive of the APS and elevated (aPL). In addition, we reviewed the literature regarding APS and APS in the context of HIV infection. **(Nazim et al., 2001)**

Thrombosis reportedly occurs in up to 2% of HIV-infected patients **(Saif et al., 2001).**

Factors associated with venous thromboembolic complications include age over 45 years, advanced stage of HIV infection, the presence of CMV or other AIDS-defining opportunistic infections, hospitalization, and therapy with indinavir or megestrol acetate **(Sullivan et al., 2000).**

The association between opportunistic infections and thrombosis may simply reflect immobility due to illness **(Saif et al., 2001).**

Alternatively, CMV may promote adhesion of neutrophils and platelets to the endothelium induce production of antiphospholipid antibodies, enhance synthesis, and increase secretion and survival of factor VIII and von Willebrand factor **(Abgueguen et al., 2003).**

Why indinavir would predispose to thrombosis is unclear, but megestrol, like other progestational agents, may cause acquired resistance to activated protein C **(Koller et al., 1999; Sullivan et al., 2000).**

In addition, individuals with HIV infection may be at increased risk for thrombosis because of decreased levels of antithrombin, free protein S, protein C, or heparin cofactor II. **(Erbe et al., 2003) .**

The presence of anticardiolipin antibodies; coexistence of malignant, inflammatory, or autoimmune disorders; or vascular damage due to injection drug use, placement of intravenous catheters, or CMV infection **(Saif et al., 2001).**

Antithrombin deficiency can occur in association with HIV nephropathy as a result of losses in the urine. The nephrotic syndrome seen in HIV nephropathy may also result in compensatory hepatic synthesis of factors V, VIII, and X induced by hypoalbuminemia, and increased platelet adhesion and aggregation **(Afsari et al., 2003).**

Acquired protein S deficiency can be found in up to 75% of HIV-infected children and adults, especially in patients with CD4 counts below 200/μL or AIDS, resulting in thrombotic complications in as many as 12% **(Erbe et al., 2003).**

Acquired free protein S deficiency in HIV is not caused by changes in levels or function of CD4-binding protein but rather by the appearance in some patients of antibodies against protein S. The levels of free protein S antigen in HIV patients can appear artificially low when assayed by the PEG precipitation technique, so that the prevalence of protein S deficiency in HIV-positive patients may actually be lower than previously thought (about 10%) **(Suvllivan et al., 2000).**

The lupus anticoagulant is found in 0%–70% of patients with HIV infection, depending on the sensitivity of the assay and the characteristics of the

patients examined. Anticardiolipin antibodies are detected in 46%-90% of these patients. Neither is strongly associated with an increased risk of venous thromboembolic complications in HIV, but events such as multiple transient ischemic attacks and stroke, avascular necrosis of bone, skin necrosis, and brachial artery thrombosis have occasionally been described in patients with anticardiolipin antibodies (**Witz et al., 2000).**

Pulmonary embolism was uncommon in this HIV infected population. The diagnosis should be considered in patients with respiratory infection which does not respond to antibiotics. Identifiable risk factors for venous thromboembolism appear to be unhelpful in increasing clinical index of suspicion for PE. As baseline chest radiographs are frequently abnormal, the diagnostic utility of ventilation/perfusion (V/P) scanning may be reduced and CT pulmonary angiography is the imaging modality of first choice. **(Howling et al., 1999).**

A plasma free protein S deficiency was detected in 41 of 63 patients infected with the human immunodeficiency virus type I (HIV-1). This study consisted in a prospective analysis of blood samples from 26 patients with confirmed diagnosis of AIDS, two with AIDS-related complex, 10 with polyadenopathy, and 25 who were asymptomatic. Protein S levels were compared to a matched control group of 24 healthy subjects. A deep venous thrombosis occurred in three AIDS patients with free protein S deficiency. A significant decrease in plasma free protein S levels was observed in HIV-1-seropositive patients (mean +/- SD, 56.5 +/- 23.3%) as compared with control subjects (105.3 +/- 18%, p = 0.0001). Free protein S levels were significantly lower in patients with full-blown AIDS (37.6 +/- 12.3%) than in patients without AIDS (69.8 +/- 19.9%, p = 0.0001). Low plasma free protein S levels correlated w ith high β 2-microglobulin values (p = 0.0001), low CD4+ T-cell counts (p = 0.0002) and elevated urinary neopterin concentrations (p =

0.005). According to a multiple regression analysis, the progression to stages IVB, IVCI or IVD of the Centers for Disease Control (CDC) appeared to be the main explanatory variable in free protein S-deficient patients. Such results suggest that free protein S deficiency may coincide with the development of AIDS. This could contribute to hypercoagulability and, in some instances, thromboembolic complications in AIDS patients. **(Bissuel et al 2003)**

Infection with human immunodeficiency virus (HIV) may lead to hemostatic imbalances. Forty-nine consecutive patients with acute opportunistic infections were screened for thrombophilic parameters. A follow-up investigation was performed after 10 weeks in 26 patients. In acutely ill patients, the incidence of protein S deficiency was 67% (33/49) and of protein C deficiency 25% (12/49), while at the follow-up visit the incidences were 54% (14/26) and 8% (2/26), respectively. Protein S and protein C levels increased significantly from initial to follow-up visit ($p < 0.05$). Lupus anticoagulants were not detected and anticardiolipin IgG antibodies were present in 11.4% (5/44). Three patients presented with deep venous thrombosis on admission; in two, protein S or protein C deficiency was observed. In conclusion, an acquired protein S and protein C deficiency often develop in patients with HIV and acute illness; this may be reversible after treatment for opportunistic infections. **(Matthias et al., 2006).**

The reported incidence of venous thromboembolism (VTE) in patients with human immunodeficiency virus (HIV) infection has ranged from 0.25 to 0.96% in clinical studies, but up to 17% at autopsy. A preliminary analysis suggested that the frequency of VTE among HIV-positive individuals might be higher than previously reported. To further evaluate this issue, we performed a retrospective study of patients with a diagnosis of VTE and/or HIV infection discharged from our hospital between July 1, 1998 and June 30, 1999. A total

of 13,496 patients were discharged during the year of the study. There were 244 patients with VTE and 362 who were HIV-positive. Ten of the 244 patients with VTE were HIV-positive (4.1%). The frequency of VTE among HIV-positive individuals was 10/362 (2.8%) compared to 234/13134 (1.8%) in the non-HIV-positive group, but the difference is not statistically significant. However, in patients under age 50, the frequencies were significantly different: 10/302 (3.31%) versus 35/6594 (0.53%), respectively ($p < 0.0001$). The frequency of VTE in HIV-positive patients less than 50 years old (3.31%) was greater than in HIV-positive patients over 50 years of age (0/60), but the difference did not reach statistical significance. In contrast, in the non-HIV-positive group, VTE was significantly more frequent in those 50 and older compared to younger patients (3.04% versus 0.53%, $p = 0.0001$). Statistical analysis indicated that the direction of association between age and diagnosis of VTE differed for HIV-positive patients versus non-HIV-positive patients. Results suggest that HIV-positive patients under age 50 are at increased risk for VTE compared with non-HIV-positive individuals (**Sinan et al., 2002).**

Previous publications have described thrombotic events with unclear causes in individuals infected with the human immunodeficiency virus (HIV).Studies were done examen the cases of 52 individuals infected with HIV by degree of immunosuppression and the presence of complicating illnesses. Plasma from these individuals was screened for abnormalities that might predispose to thromboses. Studies were done found statistically significant differences between patients with CD4 counts < 200/mm^3 and those whose CD4 counts were > 400/mm^3 in the f ollowing : d-dimers , functional protein C,antigenic protein C, total protein S antigen, free protein S antigen, C4b-binding protein (C4b-BP), and von Willebrand antigen (vWD). Free protein S correlated inversely with C4b-BP; vWD directly with total protein S; and

protein C inversely with d-dimers. D-dimers were significantly elevated only in immunosuppressed patients with complicating neoplastic/inflammatory disease. Studies were done propose that low-grade disseminated intravascular coagulopathy in severely immunosuppressed individuals with HIV and infectious, inflammatory, or neoplastic complications is responsible for depressed protein C, which, together with elevations in total protein S and vWD (markers of endothelial injury), indicates a thrombotic predisposition. **(Feffer et al., 1995).**

2- Thrombocytopenia

Shortly after the first description of the acquired immunodeficiency syndrome (AIDS), cytopenias of all major blood cell lines were increasingly recognized among patients infected with the human immunodeficiency virus (HIV). In one early series of patients with AIDS , thrombocytopenia in 40 percent **(Morris et al., 1982).**

The incidence of the various cytopenias correlates directly with the degree of immunosuppression. However, isolated abnormalities, particularly thrombocytopenia, may be encountered as the initial presentation of HIV infection. As a result, HIV infection should be considered in the assessment of patients presenting with any type of cytopenia. HIV-associated thrombocytopenia occurs in patients from all major risk groups, including those exposed via homosexual or heterosexual contact, injection drug use, and blood product transfusion.**(Karpatkin et al., 2002).**

The most common cause of this complication is known to be immune thrombocytopenic purpura (ITP), which occurs in 30% or more of patients with AIDS **(Nardi and Karpatkin, 2000).**

While slightly more prevalent in those with advanced disease, ITP typically arises early in the course of HIV infection and can be seen before other manifestations of AIDS **(Martine et al., 2009).**

Unlike the usual form of ITP, HIV-associated ITP is more frequently seen in men than women, and is commonly associated with elevated levels of platelet-associated IgG, IgM, C3C4, and circulating immune complexes. This polyethylene glycol (PEG)-precipitable serum immune complexes contain high-affinity IgG directed against an 18 amino acid peptide sequence in platelet glycoprotein IIIa known as GPIIIa **(Nardi et al., 1997).**

This antibody may be induced by HIV glycoprotein 120 and then cross-react with platelet GPIIIa, and can be found even in patients who are not thrombocytopenic **(Nardi and Karpatkin, 2000).**

In addition, patients with HIV have relatively increased numbers of $CD5^+$ B cells, which produce IgM rheumatoid factor directed against the Fc portion of IgG, as well as IgM against the F(ab´)2 fragments of anti-GPIIIa antibodies. The presence of this latter anti-idiotypic antibody has been correlated with higher platelet counts, suggesting that ITP arises in those whose dysfunctional immune systems can no longer generate sufficient antiidiotype antibody to neutralize circulating anti- GPIIIa. **(Karpatkin et al., 2002).**

Dominguez and coworkers (1994) studied platelet kinetics in 41 HIV-infected thrombocytopenic patients and found that platelet survival was lower in those with CD4 counts above 200 cells/mL than in those with counts below this level, implying that platelet destruction is more important in patients with high CD4 counts, and decreased platelet production is more important in those with lower CD4 counts. Similar kinetic studies performed by **Cole et al. (1998).** Concluded that HIV-infected patients have ineffective delivery of viable platelets to the peripheral circulation, despite a 6-fold elevation in thrombopoietin levels and a 3-fold expansion of megakaryocyte mass compared to normal controls. This finding suggests the possibility of HIV-induced

apoptosis of megakaryocytes and is compatible with the results of kinetic experiments, which found increased platelet turnover but no change in platelet survival following the initiation of zidovudine (AZT) therapy, indicating that platelet production had increased during treatment **(Karpatkin et al., 2002).**

Megakaryocyte infection by HIV is supported by the following: denuded nuclei and ballooning of the peripheral zone of megakaryocyte cytoplasm have been observed by electron microscopy; internalization of HIV particles has been seen in coculture studies; the presence of the HIV p24 antigen has been shown by immunohistochemical techniques; and expression of HIV RNA has been found using in situ hybridization. **(Li et al., 2005).**

Marrow infiltration by infectious organisms or neoplasms, as well as adverse drug effects, can also cause impaired platelet production and thrombocytopenia. Although 8% of patients with HIV-associated thrombocytopenia will have a hemorrhagic event, treatment is usually not necessary unless the platelet count is below 30,000/μL or the patient is symptomatic. **(Carbonara et al., 2001).**

Patients with hemophilia or other coagulopathies should probably receive therapy when their platelet counts are below 50,000/μL because of their higher risk of bleeding. As many as 18% of patients who have HIV-associated thrombocytopenia will undergo spontaneous remission. In those who do not, therapy historically has consisted of institution of AZT **(Ananworanich et al., 2003).**

Other treatment modalities specifically for HIV-associated ITP include glucocorticoids, intravenous IgG (IVIG), intravenous anti-D therapy, splenectomy, danazol, interferon, and vincristine. Glucocorticoids, typically prednisone 1 mg/kg daily, increase the platelet count in many patients;

however, long-term use can result in Cushing's syndrome, an increased risk of fungal infection, and acceleration of the course of Kaposi's sarcoma.1 Infusion of IVIG induces rapid but unsustained remissions in 71%–100% of HIV-infected patients, 52 but is costly and cumbersome to administer **(Novitzky et al., 2005).** Intravenous anti-D therapy is less expensive, but increases the platelet count above 50,000/μL in only 34% of patients treated. Although the response to anti-D is longer than that seen with IVIG, the extent of hemolysis in D+ (Rh+) patients is unpredictable. Patients with baseline hemoglobin levels above 12 g/dL are more likely to have a clinically important elevation of their platelet counts than those with anemia **(Scaradavou et al., 2009).**

Splenectomy can also be successful and, despite early concerns, does not obviously increase the risk of progression of HIV infection to symptomatic AIDS.In fact, a long-term cohort study of 45 patients (17 had splenectomies and 28 did not) demonstrated a significant reduction in the risk of developing full-blown AIDS and a trend toward reduced mortality in splenectomized patients **(Tsoukas et al., 1998).**

This may be due in part to a temporary reduction in plasma viremia and an increase in absolute CD4 and CD8 counts **(Bernard et al., 1998).**

Splenic irradiation is of minimal benefit, resulting only in small increases in platelet counts for brief periods of time **(Blauth et al., 1999).**

Both hemolytic uremic syndrome (HUS) and thrombotic thrombocy-topenic purpura (TTP) have been described. When compared to TTP, HUS is more likely to present at later stages of HIV disease, to be refractory to therapy, and to result in death. It is not known if HIV-associated TMA is provoked or potentiated by endothelial cell perturbation or damage, as by HIV itself, cytomegalovirus (CMV), inflammatory cytokines, or toxins produced by

Shigella dysenteriae and Escherichia coli O157:H7 **(Hymes KB and Karpatkin S., 1997).**

In 2 cases of HIV-associated TTP studied thus far, persistence of high-molecular weight von Willebrand factor multimers (vWF) and complete deficiency of vWF-cleaving protease (ADAMTS-13) were found, but in only 1 case was this due to a demonstrable IgG1 inhibitor of ADAMTS- 13 **(Sahud et al., 2002; Gruszecki et al., 2002).**

Therapy consists of plasma exchange. The response may be better in patients who have previously been splenectomized **(Hymes KB and Karpatkin S., 1997).**

3-White Blood Cells Disorders

LUCOPENIA

The most common form of leukopenia is neutropenia, or a reduced number of neutrophils. Neutrophils comprise about 45 % to 75 % of the total white blood cell count. They are responsible for fighting bacterial, fungal, viral, and parasitic infections. Neutropenia is associated with increased risk of bacterial infections. If not treated during the early infectious phase, and if the level of neutrophils falls too low, septic shock and death often occur. **(Cosby CD ., 2007).**

Diagnosis is dependent on a complet blood count (CBC) test. Neutropenia in adults is defined as an absolute neutrophil count of less than 500 cells per microliter (µL). However, even a neutrophil count of less than 1000 cells/µL of blood can raise the risk of infection .Drugs that have been associated with neutropenia are antibiotics (including penicillin) and antiretroviral drugs used

in the treatment of HIV/AIDS. Drug-induced neutropenia can often be reversed by discontinuing use of the drug **.(Levy ,2009).**

The researchers were looking at T helper cells, a class of white blood cells which recognise infection and co-ordinate the body's immune defences. They are attacked by HIV, and their numbers gradually decline in HIV positive patients. It has long been a major puzzle why this process of depletion is so slow, often taking 10 years or more**. (Coakley et al., 2005).**

One popular theory has been the "runaway" hypothesis, which says that T cells infected by HIV produce more HIV virus particles, which activate more T cells, that in turn become infected, leading to an uncontrolled cycle of T cell activation, infection, HIV production and cell destruction. However, this new study in PLoS Medicine shows that this theory cannot explain the very slow pace of depletion that occurs in HIV infection. The research team used a mathematical model of the processes by which T cells are produced and eliminated to show that if the runaway theory was correct, then T helper cell numbers would fall to very low levels over a number of months, not years. **(Deng et al., 1996).**

He said: "Scientists have never had a full understanding of the processes by which T helper cells are depleted in HIV, and therefore they've been unable to fully explain why HIV destroys the body's supply of these cells at such a slow rate. Our new interdisciplinary research has thrown serious doubt on one popular theory of how HIV affects these cells, and means that further studies are required to understand the mechanism behind HIV's distinctive slow process of cellular destruction." The research team think that one possible explanation could be that the virus slowly adapts itself over the course of the infection, but they stress that further analysis is needed to verify this alternative theory. Professor Stark adds: "If the specific process by which HIV depletes this kind

of white blood cells can be identified, it could pave the way for potential new approaches to treatment." . **(Arthos et al., 2008).**

WHAT ARE CD4 CELLS?

CD4 cells are a type of lymphocyte (white blood cell). They are an important part of the immune system. CD4 cells are sometimes called T-cells. There are two main types of T-cells. **T-4 cells**, also called CD4+, are "helper" cells. They lead the attack against infections. **T-8 cells**, (CD8+), are "suppressor" cells that end the immune response. CD8+ cells can also be killer cells that kill cancer cells and cells infected with a virus. Researchers can tell these cells apart by specific proteins on the cell surface. A T-4 cell is a T-cell with CD4 molecules on its surface. This type of T-cell is also called ?CD4 positive,? or CD4+. **(Wood et al., 2003).**

WHY ARE CD4 CELLS IMPORTANT IN HIV?

When HIV infects humans, the cells it infects most often are CD4 cells. The virus becomes part the cells, and when they multiply to fight an infection, they also make more copies of HIV.When someone is infected with HIV for a long time, the number of CD4 cells they have (their CD4 cell count) goes down. This is a sign that the immune system is being weakened. The lower the CD4 cell count, the more likely the person will get sick.There are millions of different families of CD4 cells. Each family is designed to fight a specific type of germ. When HIV reduces the number of CD4 cells, some of these families can be totally wiped out. You can lose the ability to fight off the particular germs those families were designed for. If this happens, you might develop an opportunistic infection. **(Piantadosi et al ., 2007).**

HOW ARE THE TEST RESULTS REPORTED?

CD4 cell tests are normally reported as the number of cells in a cubic millimeter of blood, or mm3. There is some disagreement about the normal range for CD4 cell counts, but normal CD4 counts are between 500 and 1600, and CD8 counts are between 375 and 1100. CD4 counts drop dramatically in people with HIV, in some cases down to zero. The ratio of CD4 cells to CD8 cells is often reported. This is calculated by dividing the CD4 value by the CD8 value. In healthy people, this ratio is between 0.9 and 1.9, meaning that there are about 1 to 2 CD4 cells for every CD8 cell. In people with HIV infection, this ratio drops dramatically, meaning that there are many times more CD8 cells than CD4 cells. Because the CD4 counts are so variable, some health care providers prefer to look at the CD4 percentages. These percentages refer to total lymphocytes. If test reports CD4% = 34%, that means that 34% of lymphocytes were CD4 cells. This percentage is more stable than the number of CD4 cells. The normal range is between 20% and 40%. A CD4 percentage below 14% indicates serious immune damage. It is a sign of AIDS in people with HIV infection. A recent study showed that the CD4% is a predictor of HIV disease progression.**(Coakley et al., 2005).**

WHAT DO THE NUMBERS MEAN?

The meaning of CD8 cell counts is not clear, but it is being studied.The CD4 cell count is a key measure of the health of the immune system. The lower the count, the greater damage HIV has done. Anyone who has less than 200 CD4 cells, or a CD4 percentage less than 14%, is considered to have AIDS according to the US Centers for Disease Control.CD4 counts are used together with the viral load to estimate how long someone will stay healthy . **(Arthos et al., 2008).**

When to start antiretroviral therapy (ART):

When the CD4 count goes below 350, most health care providers begin ART. Also, some health care providers use the CD4% going below 15% as a sign to start aggressive ART, even if the CD4 count is high. More conservative health care providers might wait until the CD4 count drops to near 200 before starting treatment. A recent study found that starting treatment with a CD4% below 5% was strongly linked to a poor outcome.

When to start drugs to prevent opportunistic infections:

Most health care providers prescribe drugs to prevent opportunistic infections at the following CD4 levels:

- **Less than 200**: pneumocystis pneumonia (PCP)
- **Less than 100**: toxoplasmosis and cryptococcosis
- **Less than 75**: mycobacterium avium complex (MAC).

Because they are such an important indicator of the strength of the immune system, official treatment guideline in the US suggest that CD4 counts be monitored every 3 to 4 months. **(Cosby ,2007)** .

The symptoms will depend on the pathogen involved, the site of the infection, and the health of the immune system , HIV-related infections may affect any part of the body. Some opportunistic infections may also cause symptoms that spread through several areas of the body. In general, the healthier the immune system, the less severe the disease. For example, tuberculosis is usually confined to the lungs in people whose immune systems are still rather strong. As the immune system weakens, tuberculosis may spread outside the lungs to other areas of the body. **(Gottlieb ,2004).**

The risk of developing opportunistic infections depends on the health of the immune system, The health of the immune system is measured by the number of a certain kind of white blood cell (CD4 cells) per microliter (µL) of blood. Certain diseases are likely to occur at different levels of CD4 counts. For example, tuberculosis and oral thrush occur even in people whose immune systems are relatively healthy (CD4 counts >200/µL), while other infections usually don't appear until late in the course of HIV disease (CD4 counts <50/µL). **(Chohan et al ., 2005).**

Table (7): Opportunistic Infections and CD4 T Cell Count in HIV Disease

CD4 Count	Disease
200-500/µL	Pneumonia (usually caused by bacteria)
	Tuberculosis in the lungs
	Oral or vaginal yeast infections
	Shingles (viral skin infection)
	Oral hairy leukoplakia
	Kaposi's sarcoma
100-200/µL	All of the above plus:
	Pneumonia due to *Pneumocystis carinii* (PCP)
	Chronic diarrhea
50-100/µL	All of the above, plus:
	Encephalitis (usually due to toxoplasmosis)
	Esophagitis due to yeast or viruses
	Meningitis (usually due to cryptococcus)
	Tuberculosis outside the lungs
	Chronic herpes simplex virus (HSV infection

	Primary brain lymphoma
<50/µL	All of the above, plus:
	Widespread infection due to *Mycobacterium avium* complex
	Retinitis, diarrhea, encephalitis due to cytomegalovirus

(Piantadosi et al., 2007).

Proinflammatory cytokines:

Play an important role both in control and pathogenesis of HIV infection. During infection, viral particles are taken up by antigen presenting cells (APCs), which are then recognized by CD4+ T lymphocytes, causing activation and release of IL-2 and IFN-gamma. These proinflammatory cytokines in turn stimulate CD8+ T lymphocytes, which control viremia. It is not known if this inflammatory response seen in HIV has an effect on the adherence and sequestration seen in malaria. However, HIV upregulates adhesion molecules on endothelial cells, which may compound the adherence and sequestration seen in malaria **(Gendelman et al., 2005).**

HIV also dysregulates pathways of cytokine expression, such that production of the proinflammatory cytokines IL-12 and IFN-gamma is decreased and expression of the anti-inflammatory cytokine IL-10 is increased. As HIV progresses clinically to AIDS there are effects on innate immunity, with progressive loss of T lymphocyte responses to common recall antigens . Increased IL-10 has been shown to play a role in this impaired innate immune response in AIDS patients. **(Ma X and Montaner L J.,2000).**

The impaired innate immune response in patients with AIDS may in part account for the increased rates of symptomatic malaria seen in cohort studies. However, the decreased production of IL-12 and IFN-gamma seen in HIV is

confounding, as high levels of these proinflammatory cytokines are associated with severe malaria in clinical studies. and previously mentioned cohort studies have found higher rates of severe or symptomatic malaria in subjects with HIV. Increased expression of IL-10 also appears to play a role in loss of adaptive immunity. IL-10 impairs T helper type 1 (Th1) responses **(Ma X and Montaner L J.,2000).**

Dendritic cells in HIV/AIDS are functionally impaired, producing less IL-12 and more IL-10, disrupting the IL-12/IFN-gamma signaling pathway and contributing to problems with adaptive immunity .It is not clear if this impairment is due to direct HIV infection of dendritic cells, or that indirect effects of chronic antigenic stimulation or exposure to virally induced proteins cause dendritic cell dysfunction. Given the important role of dendritic cells in adaptive immunity to malaria, the effects of HIV on dendritic cell dysfunction may also contribute to the higher frequency of symptomatic parasitemia seen in cohort studies. **(Yadav et al., 2009)**

Cell Kinetics in HIV Induced Immune Deficiency and Regeneration

T cell kinetics have been directly measured in HIV disease using a deuterium labeled glucose technique that has demonstrated a markedly shortened half-life of peripheral blood T cells from approximately 82 days to 23 days. **(Hellerstein et al., 1999).**

A compensatory increase in CD8+ cell production occurred, but this increase was restricted to the CD8+ fraction with no such increase not evident in the CD4+ cell pool, thereby accounting for the gradual attrition in CD4+ cells during progression to AIDS. With initiation of anti-retroviral therapy in the same study, surprisingly no improvement in lymphocyte half-life was observed (rather a decrease for both CD4+ and CD8+ cells), but a dramatic increase in T cell production occurred. The increase in T cell numbers in the

peripheral blood of treated patients appears to be dominated by improved production, a process that may be due to one of several mechanisms: expansion or redistribution of existing subsets of cells or de novo generation of newly minted T cells from the thymus. The increase in T cells following initiation of HAART is biphasic. In the interval immediately following the start of therapy, there is a prompt increase in both CD4+ and CD8+ cells that is composed predominantly of cells of a memory phenotype (CD45RO+ or CD45RA+ CD62L-). This increase is slightly different for CD4+ cells, which increase more briskly (0.027/day) and plateau at ~3 weeks compared with CD8+ cells (increase of 0.008/day), which plateau at 8 weeks. **(Pakker et al., 1998).** This increase is thought to be due largely to a redistribution from peripheral tissues perhaps related to a changing level of activation of the cells with declining viral antigen stimulation. This initial increase in circulating cell numbers does not achieve normal blood levels of lymphocytes. The secondary, much slower phase of T cell increase tends to be sustained for months to years with a greater contribution of cells with a naïve phenotype (CD45RA+ CD62L+). The naïve population rises along with cells bearing the T cell receptor excision circle (TREC), an indicator of recent T cell receptor rearrangement that accompanies early T cell differentiation. It is this population that is generally regarded as thymus dependent and that is capable of truly expanding the immune repertoire. **(Bucy et al., 1999).**

Leucopenia is defined as any situation in which the total number of leukocytes (white blood cells) in the circulating blood is less than 4000/mm^3. Granulocytes are the cells of the myeloid series and consist of neutrophils, esinophils, and basophils. Neutrophils are the most frequent and most active phagocyte among the various types of white blood cells **(Cosby, 2007).**

The incidence of leucopenia (white blood cells < 4000/mm^3) in AIDS patients ranges from 57% to 76%; leucopenia affects 19% to 41% of HIV-infected patients with lymphadenopathy. Leucopenia may also occur in the setting of acute HIV infection. Up to 44% of PWAs have granulocytopenia **(Rodgers, 1995).**

As the $CD4^+$ count falls below 100 cells/mm^3, the risk for developing granulocytopenia is increased. The Multicenter AIDS Cohort Study found that significantly fewer patients with $CD4^+$ counts greater than 700 cells/mm3 had low granulocyte counts (0.8%), compared with 13.4% of those with $CD4^+$ counts below 249 cells/mm^3 **(Cosby, 2007).**

Neutropenia (absolute neutrophil count of 500/mm^3 or less) usually occurs with anemia as HIV disease progresses. Approximately 10% of early, asymptomatic HIV-infected patients and more than 50% of those with more advanced disease are reported to have neutropenia. **(Levy et al., 2009).**

A defect anywhere in the neutrophil life cycle can lead to dysfunction and compromised host defenses. Inflammation is often depressed, and the clinical result is often recurrent and severe bacterial and fungal infections. Aphthous ulcers of mucous membranes, gingivitis, and periodontal disease are common. The most common neutropenias are iatrogenic, resulting from the widespread use of cytotoxic or immunosuppressive therapies. Neutropenia is seen in approximately half the patients with HIV infection. It is mild in most instances; however, it can be severe and place patients at risk of spontaneous bacterial infections. This is usually seen in patients receiving any of a number of myelosuppressive therapies used in the treatment of HIV infection and its complications. **(Smith, 2004).**

The majority of severe infections occur at neutrophil levels less than 500/mm^3. Unless there is an associated fever or infection, patients may be unaware that they have neutropenia. A decrease in febrile events and adecreased incidence of hospitalization have been demonstrated with the use of colony-stimulating factors (CSFs) to manage neutropenia. Concerns over the risk of decreasing the neutrophil count cause under-dosing of medications, delaying treatments, and failing to escalate doses **(Cosby, 2007).**

Recombinant G-CSF or GM-CSF can be initiated and titrated to maintain a neutrophil count > 1000/mm^3. Dosing can be done every day or every other day as needed. Clinical response is usually seen within 24 to 48 hours. These CSFs should not be used within 24 hours of chemotherapy or in myeloid malignancies and myelodysplasia. Patients may complain of bone pain during therapy with these CSFs **(Tang et al., 2003).**

4- Hematological Neoplasm

Lymphoma

Lymphoma has traditionally been considered a late manifestation of HIV infection, more likely to occur in the setting of significant immune suppression with CD4 cells below 200/mm^3 , and prior history of an AIDS defining illness. Thus, following an earlier diagnosis of AIDS, the relative risk of immunoblastic lymphoma is approximately 627-fold increased, while that of diffuse large cell lymphoma is 145-fold increased, over that expected in the general population**.(Grulich et al., 2001).**

Of interest, when linking cancer and AIDS registries, even low grade lymphoma was found to be increased 14-fold over that expected in individuals who had already been diagnosed with an AIDS defining illness. while the incidence of T cell lymphoma has also increased among patients with AIDS. **(Biggar et al., 2001) .**

While HAART therapy has been associated with a significant decline in the incidence of various opportunistic infections and Kaposi's sarcoma , such a major and significant decline has not yet been uniformly described in regards to systemic AIDS-lymphoma. In a cohort of 6,636 HIV infected individuals from Switzerland, reflecting over 18,000 patient-years of follow-up, no decrease in lymphoma was seen when comparing the periods 1992-1994 (prior to the widespread use of HAART) with the period from July 1997 to June 1998**.** A recent report of over 7,300 HIV infected patients from 52 European countries compared data on AIDS defining illnesses diagnosed during 1994, prior to the HAART era, with those diagnosed in 1998, after widespread use of HAART in these regions. The incidence of AIDS defining conditions declined from 30.7/100 patient-years in 1994 to 2.5/100 patient-years during 1998 ($p < 0.0001$). However, while the proportion of new AIDS cases due to various opportunistic infections decreased, the proportion of new AIDS secondary to lymphoma increased significantly, with lymphoma representing less than 4% of all AIDS diagnosed in 1994 and 16% of all AIDS diagnosed in 1998 ($p < 0.0001$). In contrast, there was no evidence for an increase in the proportion of AIDS diagnosis due to primary central nervous system lymphoma **(Mocroft et al., 2000).**

An international collaborative study, including cancer incidence data from 23 prospective studies that included 47,936 HIV seropositive individuals from North America, Europe and Australia, sought to determine the adjusted incidence rates of various AIDS defining conditions since the advent of HAART. In terms of lymphoma incidence, the rate ratio showed a significant reduction when cases diagnosed in 1992-1996 were compared with those from 1997-1999. Of interest, however, the rate ratio for immunoblastic lymphoma

and primary central nervous system lymphoma declined significantly during these two time intervals, while that of Burkitt's lymphoma and Hodgkin's disease (HD) showed no such decline **(National Cancer Institute., 2000).**

Taken together, these data would suggest that the incidence of primary central nervous system and systemic lymphoma have decreased since the widespread use of HAART. However, the decline in lymphoma is far less impressive than that observed for opportunistic infections or Kaposi's sarcoma, resulting in a proportionate increase in lymphoma as an initial AIDS defining illness. Furthermore, while initial controlled clinical trials have indicated that approximately 80% of treated subjects will achieve a non-detectable HIV viral load after HAART therapy, only approximately 40% will achieve this end-point in "real world" conditions. The effect of HAART on the incidence of AIDS lymphoma will clearly be dependent upon the long-term efficacy of combination anti-retroviral therapy when assessed at the population level. Issues of access, compliance, drug resistance and underlying host and environmental factors will all likely be operative. Further time will thus be required to elucidate the full impact of HAART on the incidence of AIDS-related systemic and primary CNS lymphoma. **(Lucas et al., 1999).**

Genetic Epidemiology of AIDS-Related Lymphoma

In distinction to Kaposi's sarcoma, which occurs primarily in men who have sex with men, lymphoma is seen in all population groups at risk for HIV. Similar to de novo lymphoma occurring in HIV negative individuals, AIDS lymphoma is more common in men than in women. All age groups are affected, and lymphoma is the most common malignancy in HIV infected children. Epidemiologic studies have failed to identify major environmental factors

associated with AIDS lymphoma among HIV infected individuals. However, host genetic factors may be operative. Thus, HIV infected patients who are heterozygotes for the CCR5D32 deletion are statistically less likely to develop lymphoma, while those with SDF-1 mutations (3'A) are statistically more likely to develop lymphoma. **(Rabkin et al., 1999).**

Changing Characteristics of Patients with AIDS-Lymphoma in the Era of HAART:

There is some inconsistency regarding potential changes in the clinical or pathologic characteristics of patients with AIDS-lymphoma since the widespread use of HAART. These inconsistencies may be related to differing patient populations, access to HAART, or other unknown factors. Levine reviewed records of 369 patients diagnosed with AIDS-lymphoma at a single institution from 1982 through 1998 and compared these data to population-based information from the County of Los Angeles. Significant changes in the demographic characteristics of AIDS-lymphoma occurred in both populations, with the latter time period characterized by statistically significant increases among women, Latino/Hispanic individuals, and those who acquired HIV heterosexually. The median CD4+ lymphocyte count at the time of lymphoma diagnosis decreased significantly over the years, with a median count of 177/mm^3 in the earliest time period and 53/mm^3 in the latest **(Levine et al., 2000).**

A decrease in small non-cleaved (Burkitt or Burkitt-like) lymphomas occurred over time, while the prevalence of diffuse large cell lymphoma increased. Despite changes in the use of anti-retroviral and anti-neoplastic therapy, the median survival did not change appreciably over time. Similarly,

Matthews reporting on experience in London, UK, with 7840 HIV positive patients, representing over 43,000 patient-years of follow-up, noted no change in the median survival of patients with AIDS-related lymphoma, diagnosed between 1988-1995 and 1996-1999 **(Matthews et al., 2000).**

While the incidence of AIDS-lymphoma did not change over time, lymphoma became more common as an initial AIDS-defining illness. On multivariate analysis, characteristics statistically associated with development of AIDS-lymphoma included lower CD4 lymphocyte counts (both at baseline and at nadir), older age, and lack of HAART therapy. In a study of HIV infected patients followed in Paris, France, the incidence of AIDS-lymphoma has decreased since the advent of HAART, and the median CD4 cell count at lymphoma diagnosis has increased significantly, from 63/mm^3 in the earliest to 191/ mm^3 in the latest time interval. **(Pallella et al 1998**).

Coincident with these changes, the median survival of 145 patients with AIDS lymphoma statistically increased over time. Of great interest, while the overall incidence of AIDS-lymphoma decreased, when evaluated by specific CD4 lymphocyte count or strata, no change in the incidence of lymphoma was apparent. Thus, the decrease in overall incidence of AIDS-lymphoma was driven by the fact that CD4 lymphocyte counts had increased, presumably due to the widespread use of HAART. These studies would indicate that the successful use of highly active anti-retroviral therapy may be associated with higher CD4 lymphocyte counts and an increased survival of patients with AIDS-lymphoma. At the same time, the improvement in immune function has also been associated with a decrease in the over-all incidence of lymphoma **(Besson et al., 2001).**

Prognostic Factors in Patients with Systemic AIDS-Related Lymphoma

The factors associated with shorter survival of patients with AIDS-related lymphoma include CD4 cells < 100/mm^3 , stage III or IV disease, age > 35 years, history of injection drug use, and elevated LDH. The International Prognostic Index (IPI) for aggressive lymphoma has also been validated in patients with AIDS-lymphoma. **(Rossi et al., 1999).**

Hodgkin's Disease in the Setting of HIV Infection

While not considered an AIDS-defining illness, the incidence of Hodgkin disease (HD) is clearly increased among HIV infected individuals. Unusual clinical and pathologic characteristics of HD have been described in this setting. Thus, systemic "B" symptoms are almost always present, mixed cellularity HD is the predominant pathologic sub-type of disease, and advanced, extra-nodal disease is expected in the majority. Bone marrow involvement has been documented in 40-60% of patients at initial diagnosis, and patients often undergo the initial diagnostic bone marrow examination for the evaluation of fever of unknown origin in the setting of HIV infection and pancytopenia. **(Levine et al., 2000).**

While standard multiagent chemotherapy may be curative in most HIV negative patients with stage III or IV HD, the median survival for HIV infected patients has been in the range of 1 to 2 years . A recent prospective multi-institutional trial evaluated the use of the standard dose ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen with hematopoietic growth factor support in a group of 21 HIV infected patients. Anti-retroviral therapy was not used. **(Spina et al., 2001).**

Neutropenia to levels < 500 cells/mm^3 developed in almost 50% and median survival for the group was only 18 months. It is possible that results would have improved with concomitant use of highly active anti-retroviral therapy (HAART), as was demonstrated with the Stanford V regimen, employed in 50 HIV infected patients from Italy. In this study, complete remission was attained in 78%, and 68% of these (i.e. 53% of all patients treated) are estimated to remain disease free at 2 years. Grade 3 or 4 neutropenia occurred in 82%, despite use of G-CSF. Further work will be required to define the optimal therapy for such patients. (**Grulich et al., 1999).**

5-Hemophagocytic Syndrome

The hemophagocytic syndrome is an uncommon complication of HIV infection that is characterized by proliferation of histiocytes and phagocytosis of marrow blood cell precursors. It typically presents with fever, pancytopenia, lymphadenopathy, and splenomegaly. Hemophagocytosis may also complicate malignancies like T cell non-Hodgkin's lymphoma or Kaposi's sarcoma **(Fardet et al., 2003).**

The hemophagocytic syndrome was first described in 1979 in immunosuppressed patients with viral infections. EBV is the most common etiology, while CMV is associated with 30% to 40% of all virus-associated Hemophagocytic Lympho Histocytosis (HLH) cases This syndrome is a result of damage caused by cytotoxic activity of natural killer (NK) cells and T cells; thus the ineffective immune system is constantly stimulated to generate high levels of cytokines, such as tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ), which stimulate the defense cells. High levels of cytokines are responsible for the clinical picture. HLH is an uncommon and frequently undiagnosed event, recently described in critically-ill patients **(Janka G.E et al., 2007)**

It remains a diagnostic challenge, as the clinical presentation of this condition mimics sepsis, a frequent syndrome in ICU patients , Laboratorial tests for diagnosis, such as serum triglyceride, ferritin and fibrinogen levels, are frequently not performed in the ICU, and they lack specificity, as they may be significantly altered as a result of critical illness. Moreover, blood transfusions may mask pancytopenia. Our patient had at least four conditions associated with the development of HLH (HIV infection, Burkitt's lymphoma, bacterial sepsis and CMV infection). The association of HLH and HIV has been described; however, it occurs less frequently than previously expected **(Pastore et al., 1999)**

HIV-positive patients with lymphoma are at high risk for HLH **(Janka G.E et al., 2007)**.

The association between bacterial infection and HLH is poorly documented, and most case reports indicate that it is due to intracellular bacteria (e.g. Mycobacteria, Legionella sp.) Finally, although other factors could cause HLH. Resultes believe that CMV was the main etiologic agent involved. The prompt response to ganciclovir allowed clinical and hematological improvement and ICU discharge. This case emphasizes the importance of bone marrow examination and extensive investigation for opportunistic infections in immunocompromised patients presenting with febrile pancytopenia. In most cases, treatment of the underlying condition promotes complete remission of the clinical picture.**(Fisman et al., 2000)**.

6-Blood vessles:

HIV positive people taking combination antiretroviral therapy (HAART) have an elevated risk of cardiovascular disease, but the underlying mechanisms are not well understood. Several studies have linked specific HIV drugs to

impaired blood vessel function, elevated blood lipid and glucose levels, and other cardiovascular risk factors, while others have not seen these effects. Furthermore, since HIV itself appears to contribute to elevated cardiovascular risk (for example, by increasing systemic inflammation), HAART also may have a protective effect. HIV infection itself not short-term HAART appears to be the culprit causing blood vessel damage in people with HIV, according to a study published in the March 13, 2009 issue of AIDS. Daniela Francisci and colleagues from Italy assessed whether individuals with chronic HIV infection are more likely to experience endothelial dysfunction (disruption of the lining of the blood vessels) and platelet activation.Two indicators of atherosclerosis, or buildup of plaque and "hardening of the arteries, and whether this is attributable to infection itself or to HAART. Short-term treatment with HAART reduces some markers of endothelial dysfunction, with no differences between protease inhibitors and non-nucleoside reverse transcriptase inhibitors. **(Francisci et al., 2009).**

Several studies have observed impaired endothelial function in HIV positive people on Protease Inhibitors (PI)-containing antiretroviral therapy, possibly due to elevated cholesterol and triglyceride levels. The PI atazanavir (Reyataz) is less associated with atherogenic (promoting atherosclerosis) lipid changes, and researchers have studied switching to atazanavir as a strategy for reducing cardiovascular risk. In the present study, published in the May 2009 issue of Heart, Andreas Flammer and colleagues sought to determine whether endothelial function improves after switching from another PI to atazanavir. The patients had suppressed HIV viral load on a PI-containing HAART regimen and had fasting low-density lipoprotein (LDL) cholesterol levels greater than 3 mmol/L. Participants were randomly assigned to continue on their current PI or change to unboosted (without ritonavir) atazanavir.

Endpoints at week 24 were endothelial function assessed by flow-mediated dilation (FMD, or ability of blood vessels to expand according to the amount of blood flow) of the brachial artery, blood lipid profiles, and blood markers of inflammation and oxidative stress. Based on these findings, the investigators concluded, "The switch from another PI to atazanavir in treatment-experienced patients did not result in improvement of endothelial function despite significantly improved serum lipids. Atherogenic lipid profiles and direct effects of antiretroviral drugs on the endothelium may affect vascular function **(Flammer et al., 2009).**

Finally, as described in the April 15, 2009 Journal of Infectious Diseases, Marit van Vonderen and colleagues from the Netherlands studied changes in blood vessel properties after initiation of HAART, as well as the contribution of different drug classes. Femoral artery stiffness increased after the initiation of combination ART, whereas several markers of endothelial function improved, regardless of the composition of combination ART . These findings suggest that antiretroviral therapy may have both detrimental and beneficial influences on cardiovascular risk factors, worsening atherosclerosis while improving inflammation , which may in effect partially cancel each other out.

(MGA van Vonderen et al., 2009).

7-Stem Cells in HIV Infection

Fundamental to the pathophysiology of acquired immunodeficiency syndrome (AIDS) is the inability of the immune system to compensate for the depletion of specific immune effector cells induced by HIV-1 (HIV). By targeting the cells responding to it, HIV undermines the immune response favoring viral spread in a self-accelerating manner. Yet, for some individuals the immune system remains vigorous and capable of controlling HIV. The

balance between host response and viral replication is critical in determining whether HIV persists silently or progressively erodes immune function. Anti-retroviral medication can diminish the rapidity of viral spread but does not appear able to restore critical, virus-controlling immunity. Except in cases where anti-retrovirals were begun during acute infection, **(Rosenberg et al., 2000)**.

There is little evidence that the immune recovery observed with anti-retrovirals is sufficient to permit immune control of HIV without medications. Strategies to overcome this problem and regenerate vigorous HIV-specific immunity focus on two basic goals: 1) To provide additional anti-HIV protection to developing cells; or 2) To enhance generation of specific T cell subsets. Potent, new anti-viral drugs and vaccines are respectively regarded as leading methods to achieve these goals. Autologous cells manipulated ex vivo and adoptively provided to alter the balance in favor of host control of HIV is a plausible alternative. Achieving any of these in a chronically infected host is in part contingent upon understanding the impact of HIV on both stem cells and thymic function influencing immune reconstitution. **(Hellerstein et al., 1999).**

Of concern in the setting of stem cell gene therapy is the ability to achieve transduction of a population that will ultimately be the most relevant for affecting the pathophysiology of HIV disease. In vitro systems to induce stem cell expansion are critical for permitting gene transfer into these cells, and some of the systems used in this context may affect the lineage outcome of the cells. For example, it has been noted that the presence of serum in the culture, flt-3 ligand or IL-3 may influence stem cell and lymphoid versus myeloid outcomes **(Rossi et al., 1999).**

Alternative strategies are being considered using the stem cell effects of other agents such as Notch ligands. Activation of Notch influences T lymphoid differentiation and may affect, stem cell lymphoid lineage choice if used in stem cell expansion techniques. Enhancing T lymphoid regeneration is an obviously desirable goal that stem cell expansion strategies may ultimately be tailored to achieve. In addition, ex vivo T differentiation systems are being developed**. (Ratner et al., 2001).**