

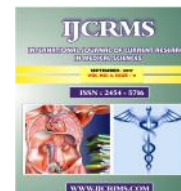


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Human Immunodeficiency Virus infection and cardiovascular disease

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Abstract

The human immunodeficiency virus (HIV) is a retrovirus belonging to the family of lentiviruses. Retroviruses are so named because they reverse the normal flow of genetic information. In all cellular organisms the genetic material is DNA. Retroviruses use their RNA and host DNA to make viral DNA. Infection with HIV causes severe damage to the immune system leading to Acquired Immune Deficiency Syndrome (AIDS). Individuals infected with HIV show both cellular and humoral (antibody) immune responses to the virus, but these responses are unable to prevent the ultimate progression of disease in the great majority of infected individuals. Depletion of CD4 lymphocytes is the hallmark of HIV infection, and predicts an individual's risk for infection with opportunistic pathogens as well as other complications of HIV disease. There is a great association of HIV and cardiovascular disease due to a higher prevalence of underlying traditional cardiovascular risk factors that are mostly host dependent. Most of the HIV drugs increase the chances of cardiovascular diseases in the patients especially protease inhibitors. Chronic inflammation, hypercoagulability and platelet activation all contribute to endothelial dysfunction, and are a probable link between HIV and cardiovascular disease.

Keywords: human immunodeficiency virus, immunity, cardiovascular disease

Introduction

The human immunodeficiency virus (HIV) is a retrovirus belonging to the family of lentiviruses. Retroviruses are so named because they reverse the normal flow of genetic information. In all

cellular organisms the genetic material is DNA. DNA passes its information to RNA, which in turn translates this information into the precise construction of proteins, whose building blocks are amino acids (Lusso, 2006). Retroviruses use their RNA and host DNA to make viral DNA.

Infection with HIV causes severe damage to the immune system leading to Acquired Immune Deficiency Syndrome (AIDS). Transmission of HIV Infection can be through sexual, parienteral or perinatal route. After initial contact and attachment to a cell of the immune system, there is a cascade of intracellular events. The end product of these events is the production of massive numbers of new viral particles, death of infected cells and ultimate devastation of the immune system (Honda and Oka, 2006). CD4 cells are the T helper cells that lead the attack against infections. They form an important component of immune response and are the primary targets of HIV. Months to years after a person is infected with HIV, the virus destroys all the CD4 cells which disables the immune system to defend the body against diseases and tumors. Various infections will be able to develop, these infections which normally do not cause severe or fatal health problems will eventually cause the death of the HIV patient (Montero *et al.*, 2005).

History of HIV and AIDS

The origin of HIV and AIDS has puzzled scientists ever since the illness first came to light in the early 1980s. For over twenty years it has been the subject of fierce debate and the cause of countless arguments. The first recognized cases of AIDS occurred in the USA in 1981 when a number of gay men in New York and California suddenly began to develop rare opportunistic infections and cancers that seemed stubbornly resistant to any treatment. At this time, AIDS did not yet have a name, but it quickly became obvious that all the men were suffering from a common syndrome. Awareness that a significant epidemic was developing grew as case reports mounted and similar immune deficiency syndromes were described elsewhere among homosexual men, intravenous drug users, Haitians, hemophiliacs, recipients of blood transfusions, infants, female sexual partners of infected men, prisoners, and Africans (Lemey, 2003). As researchers began to describe the epidemiology and risk factors in a systematic way, many theories emerged regarding the cause of the mysterious disease. An infectious agent

was postulated, and, in 1983, a novel human retrovirus was isolated as the putative etiologic agent. That virus was eventually named Human Immunodeficiency Virus, (HIV). As researches continued, the viral family lentiviruses where HIV belongs were found in a number of different animals, including cats, sheep, horses and cattle. However, the most interesting lentivirus in terms of the investigation into the origins of HIV is the Simian Immunodeficiency Virus (SIV) that affects monkeys. It is believed that HIV is a descendant of a Simian Immunodeficiency Virus because certain strains of SIVs bear a very close resemblance to HIV-1 and HIV-2 (Wainberg, 2004).

Also, HIV-2 corresponds to *SIVsm*, a strain of the Simian Immunodeficiency Virus found in the sooty mangabey (also known as the White-collared monkey), which is indigenous to western Africa. Researchers claimed that these primates were the source of HIV, and that the virus had at some point crossed species from chimps to humans through a process known as zoonosis. This gave rise to several theories but the most acceptable was the 'hunter' theory. In this scenario, *SIVcpz* (Simian Immunodeficiency Virus found in the chimpanzee) was transferred to humans as a result of chimps being killed and eaten or their blood getting into cuts or wounds on the hunter (Gao, 1999).

The extention of the 'hunter' theory was the 'The Contaminated Needle Theory'. In the 1950s, the use of disposable plastic syringes became commonplace around the world as a cheap, sterile way to administer medicines. However, to African healthcare professionals working on inoculation and other medical programmes, the huge quantities of syringes needed would have been very costly. It is therefore likely that one single syringe would have been used to inject multiple patients without any sterilisation in between. This would rapidly have transferred any viral particles (within a hunter's blood for example) from one person to another, creating huge potential for the virus to mutate and replicate in each new individual it entered, even if the SIV within the original person infected had not yet converted to HIV (Wolfe,2004).

Another theory on how HIV crossed species (zoonosis) was the 'colonialism theory'. The colonialism or 'Heart of Darkness' theory, is one of the more recent theories to have entered into the debate. It is again based on the basic 'hunter' premise, but more thoroughly explains how this original infection could have led to an epidemic. It was first proposed in 2000 by Jim Moore, an American specialist in primate behaviour, who published his findings in the journal *AIDS Research and Human Retroviruses* (Chitnis *et al.*, 2000). During the late 19th and early 20th century, much of Africa was ruled by colonial forces. In areas such as French Equatorial Africa and the Belgian Congo, colonial rule was particularly harsh and many Africans were forced into labour camps where sanitation was poor, food was scarce and physical demands were extreme. These factors alone would have been sufficient to create poor health in anyone, so SIV could easily have infiltrated the labour force and taken advantage of their weakened immune systems to become HIV. A stray and perhaps sick chimpanzee with SIV would have made a welcome extra source of food for the workers (Stahl-Hennig *et al.*, 1999; Zhu, 1998).

Until recently, the origins of the HIV-2 virus had remained relatively unexplored. HIV-2 is thought to come from the SIV in Sooty Mangabeys rather than chimpanzees, but the crossover to humans is believed to have happened in a similar way (i.e. through the butchering and consumption of monkey meat). It is far rarer, significantly less infectious and progresses more slowly to AIDS than HIV-1. As a result, it infects far fewer people, and is mainly confined to a few countries in West Africa (Gross, 2004).

Despite dramatic advances in basic virology and clinical management, HIV infection has developed into a worldwide pandemic, with tens of millions of individuals infected by the virus and many millions more affected by it (Coffin, 1999). Clinicians treating HIV are challenged by a clinically complex illness with relatively limited resources for treatment in most settings. By 1985, serologic assays had been developed to test for HIV infection in asymptomatic persons, to identify new infections by seroconversion, and to

screen blood donations (Zimmerman *et al.*, 2002). Early trials of antiretroviral treatments for HIV and immune modulators were fraught with disappointment. In 1987, zidovudine (AZT, or azidothymidine) became the first drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of AIDS. Early excitement over the life-extending effects of the drug soon waned, as patients treated with this single-drug therapy began to experience disease progression leading in most cases, to death. However, understanding of the epidemiology, treatment, and prophylaxis of opportunistic infections (OIs) associated with HIV-induced immune deficiency led to significant life-saving advances, particularly in the areas of infection with *Pneumocystis jiroveci* and *Mycobacterium avium* complex (MAC).

The introduction of protease inhibitors (PIs) in the mid-1990s revolutionized the treatment of HIV (Hammer *et al.*, 2006). Effective combination antiretroviral therapy (ART) became the standard of care in the United States and Western Europe. Thereafter, countries in which effective ART was available began to note sharply declining morbidity and mortality associated with HIV infection (Kahn *et al.*, 2001). Studies of patients receiving the new therapies shed light on HIV pathogenesis. Patients treated with potent ART showed precipitous decreases in the amount of HIV RNA circulating in their serum, indicating interference with HIV replication (which, unimpeded, can produce more than 10 billion viral particles per day). Additionally, after successful inhibition of viral replication, CD4 T-cell counts began to increase in treated individuals, demonstrating the regenerative capacity of the damaged immune system. Corroborating this understanding of the dynamic interaction between viral replication and the host immune system, studies began to show the value of HIV RNA measurement (viral load) as both a predictor of disease progression and a measure of treatment success (Althoff *et al.*, 2010; Hecht *et al.*, 2002).

However, potent therapy was not without complications, it was later realized that long-term medication toxicity was likely among individuals who were then living longer, healthier lives with

HIV infection. Once again, the paradigm of HIV treatment underwent revision, and treatment was then recommended primarily for individuals with more advanced disease (Oxenius *et al.*, 2000; Rosenberg *et al.*, 2000).

HIV types and subtypes

There are two types of HIV: HIV-1 and HIV-2. Both types are transmitted by sexual contact, through blood, and from mother to child, and they appear to cause clinically indistinguishable AIDS. However, it seems that HIV-2 is less easily transmitted, and the period between initial infection and illness is longer (Lemey, 2003; Martinez, 2006). Worldwide, the predominant virus is HIV-1, and generally when people refer to HIV without specifying the type of virus they will be referring to HIV-1. The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere. The strains of HIV-1 can be classified into four groups: the "major" group M, the "outlier" group O and two new groups, N and P. These four groups may represent four separate introductions of simian immunodeficiency virus into humans (Chalmet, 2010; Rachinger, 2011). Group O appears to be

restricted to west-central Africa and group N - a strain discovered in 1998 in Cameroon is extremely rare. In 2009 a new strain closely relating to gorilla Simian Immunodeficiency Virus was discovered in a Cameroonian woman. It was designated HIV-1 group P. More than 90 percent of HIV-1 infections belong to HIV-1 group M. Within group M there are known to be at least nine genetically distinct **subtypes** (or clades) of HIV-1. These are subtypes A, B, C, D, F, G, H, J and K (Fox, 2010). Occasionally, two viruses of different subtypes can meet in the cell of an infected person and mix together their genetic material to create a new hybrid virus (Gross, 2004; Fultz, 2004). Many of these new strains do not survive for long, but those that infect more than one person are known as "circulating recombinant forms"(CRFs). For example, the CRF A/B is a mixture of subtypes A and B (Chamet, 2010). The classification of HIV strains into subtypes and CRFs is a complex issue and the definitions are subject to change as new discoveries are made. Some scientists talk about subtypes A1, A2, A3, F1 and F2 instead of A and F, though others regard the former as sub-subtypes.

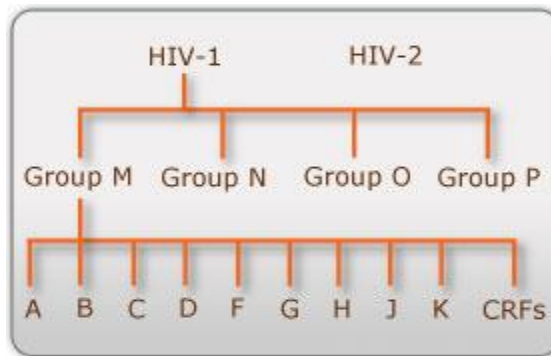


Figure 2.1: HIV Types and Subtypes (Adapted from Fox (2010)).

A person can be co-infected with different subtypes. The following are HIV-1 subtypes and their geographic distributions:

- Subtype A: Central Africa, sub-Saharan Africa
 - Subtype B: South America, Brazil, United States, Thailand, Europe, Caribbean, India, Japan
 - Subtype C: Brazil, India, South Africa
 - Subtype D: Central Africa, sub-Saharan Africa
 - Subtype E: Thailand, Central African Republic, Southeast Asia
 - Subtype F: Brazil, Romania, Democratic Republic of Congo (Zaire)
 - Subtype G: Democratic Republic of Congo (Zaire), Gabon, Thailand, Russia, Central Africa
 - Subtype H: Democratic Republic of Congo (Zaire), Gabon, Russia, Central Africa
 - Subtype I: Cyprus
 - Subtype O: Cameroon, Gabon (Fox, 2010).
- Subtypes are unevenly distributed throughout the world. Subtype C currently accounts for more than half of all new HIV infections worldwide. Africa has most subtypes, although subtype B is less prevalent. There are no known subtypes of HIV-2 (Chalmet, 2010).

Virology

HIV-1 and the less common HIV-2 belong to the family of retroviruses. HIV-1 contains a single-stranded RNA genome that is 9 kilobases in length and contains 9 genes that encode 15 different proteins (Mann *et al.*, 2014). The major viral proteins (some of which contain >1 protein subunit) are classified as structural proteins (Gag, Pol, and Env), regulatory proteins (Tat and Rev), and accessory proteins (Vpu, Vpr, Vif, and Nef) (Greenway *et al.*, 2002). HIV infection of a host cell begins with the binding of the virus particle (virion) to the host cell. This process is initiated when the surface envelope protein (Env, which consists of 3 copies each of the 2 subunit proteins gp120 and gp41) engages its primary receptor, the CD4 molecule on the surface of the target cell. Initial binding to CD4 exposes another portion of the Env trimer, which then binds to a coreceptor, usually the chemokine receptor CXCR4 (in the case of T-cell-tropic, or syncytium-inducing strains of HIV) or the chemokine receptor CCR5 (in the case of macrophage-tropic, or

nonsyncytium-inducing strains). This coreceptor binding causes the gp41 trimer portion of the envelope molecule to spring open and "harpoon" the lipid bilayer of the target cell membrane. The "hairpin" domains of gp41 then fold together to pull the virus and host cell membranes together, allowing fusion to occur. The viral contents, including copies of the viral genetic material and the Pol protein (reverse transcriptase, or RT) thus enter the cytoplasm of the host cell. Reverse transcription, that is, the copying of the viral genetic material from RNA into DNA can then occur (Fultz, 2004).

The preintegration complex (PIC), composed of the copied DNA (cDNA) and a number of viral and host proteins, then enters the cell nucleus, where the viral enzyme integrase mediates the insertion of the viral cDNA into the host chromosomal DNA. The resulting integrated DNA virus (also called a provirus, to distinguish it from the virion form) may remain latent for hours to years before becoming active through transcription (copying of DNA into RNA). Transcription of the viral genome is under complex control of a number of proteins, including Tat and cellular DNA transcription factors (Weber, 2001). Transport of the transcribed viral RNA out of the nucleus also depends on a number of host and viral factors, including Rev. The transcribed viral RNA may be transported out of the nucleus in its full-length form to serve as genetic material for new virions, or it may be partially or fully spliced. The unspliced, partially spliced, and fully spliced versions of viral RNA direct the synthesis of different viral proteins by the cell ribosomes. New viral particles are assembled at the plasma membrane and incorporate Gag subunits, Pol, Nef, Env, Vpr, and viral genomic RNA. The HIV viral protease enzyme acts following virion assembly to cleave viral proteins into functional structural and enzymatic components. Gag then functions in the budding of mature virions from the plasma membrane. The Nef protein acts on the cellular environment to promote replication by inhibiting the host immunologic response to HIV and inhibiting death of infected cells by apoptosis (Mann *et al.*, 2014).

Immunology of HIV

Individuals infected with HIV show both cellular and humoral (antibody) immune responses to the virus, but these responses are unable to prevent the ultimate progression of disease in the great majority of infected individuals. Cellular responses are mediated by Cytotoxic Lymphocytes CTLs (CD8 cells) and helper T lymphocytes (CD4 cells). CTLs inhibit HIV replication both directly, by recognizing and killing infected cells, and indirectly, by producing soluble chemokine antiviral factors (Mann *et al.*, 2014).

CTL-mediated killing of virally infected host cells occurs through direct contact, whereby the T-cell receptor on the surface of the CTL recognizes a fragment (epitope) of an HIV protein bound to a major histocompatibility complex (MHC) class I molecule on the surface of the infected host cell. After this interaction, the CTL releases enzymes that kill the infected cell. CTL responses directed against certain epitopes of the Gag protein have been associated with slower HIV disease progression than CTL responses against other epitopes. CTLs also exert effects through soluble factors such as RANTES, macrophage inflammatory protein (MIP)-1-alpha, and MIP-1-beta, which inhibit HIV from infecting new cells by blocking HIV coreceptors. CD4 responses to HIV are important in viral control, and strong HIV-specific CD4 responses are associated with lower HIV viral loads (El-Sadr *et al.*, 2005). CD4 cells respond to HIV antigens presented in conjunction with MHC class II molecules on the surface of infected cells. The fact that HIV infects CD4 cells themselves is an evolutionary strategy with a number of consequences. Because

productive HIV infection occurs in activated CD4 cells, infection and killing of CD4 cells that are responding to HIV infection itself may cause a selective decrease in the number of HIV-specific CD4 cells. (HIV can also exist in nonactivated CD4 cells in a preintegrated form, which can become integrated if activation occurs within a few days. (Rodrigues *et al.*, 2006) Additionally, as some of the activated, infected CD4 cells differentiate into resting memory CD4 cells, they may carry copies of the HIV genome in a post integrated form that can persist for decades. Current antiretroviral medications cannot efficiently eliminate the virus from cells in the resting state, leading to persistence of infection even in the presence of suppressive therapy. Moreover, HIV continues to evolve under the selection pressure of the immune response that occurs in each infected individual, and mutations in the viral epitopes recognized by the immune system may enable the virus to escape the control of even broad and robust CD4 and CD8 HIV-specific responses (Kaplan *et al.*, 2007)

Depletion of CD4 lymphocytes is the hallmark of HIV infection, and predicts an individual's risk for infection with opportunistic pathogens as well as other complications of HIV disease. Evidence has shown that both increased peripheral destruction and decreased production of CD4 cells likely play a role in this decline. Humoral immunity appears to be less effective in controlling viremia than cellular responses, as HIV is remarkably effective at evading host antibody responses, and broadly neutralizing antibodies are rare. The difficulty in eliciting broadly neutralizing antibody responses against HIV has posed a particularly difficult challenge to the development of a protective HIV vaccine.

HIV STRUCTURE

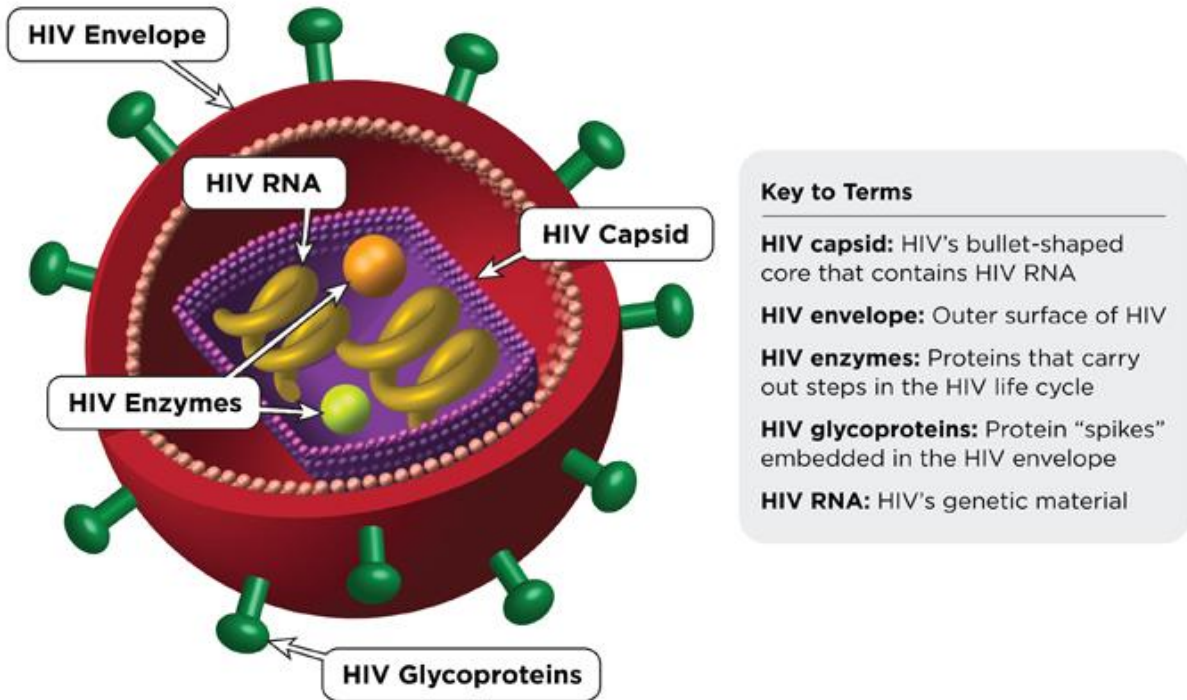


Figure 2.2: HIV Structure (Adapted from Hare, (2009))

HIV consists of a cylindrical center surrounded by a sphere-shaped lipid bilayer envelope. There are two major viral glycoproteins in this lipid bilayer, gp120 and gp41. The major function of these proteins is to mediate recognition of CD4⁺ cells and chemokine receptors, thereby enabling the virus to attach to and invade CD4⁺ cells. The inner sphere contains two single-stranded copies of the genomic material, RNA, as well as multiple proteins and enzymes necessary for HIV replication and maturation: p24, p17, reverse transcriptase, integrase, and protease. Unlike other retroviruses, HIV uses nine genes to code for the necessary proteins and enzymes. The three principal genes are gag, pol, and env. The gag gene encodes core proteins. The pol gene encodes the enzymes reverse transcriptase, protease, and integrase. The env gene encodes the HIV structural components known as glycoproteins. The rest of the genes—rev, nef, vif, vpr, and tat—are important for viral replication and enhancing HIV's infectivity rate.

Tropism and life cycle

Different viruses have different affinity for different types of cells in the body. This affinity (tropism) has to do with the existence of structures on the virus that get attracted and attached to specific structures on the chosen or target cells. The target cell for HIV is a sub population of T-lymphocytes bearing a molecule called CD4. A cell bearing this molecule is said to be CD4-

positive or CD4⁺. The letters “CD” stand for “cluster of differentiation”, which identifies a particular T-lymphocyte sub-population (Montero and Nadler, 2005). Although the T-4 lymphocytes are the main target of HIV, other cells such as macrophages and glial cells of the brain are also attacked by the virus, and are thought to bear the CD4 receptor or molecule similar to it. Host cells infected with HIV have a shortened life span as a result of the virus's using them as “factories” to produce multiple copies of new HIV. Thus, HIV continuously uses new host cells to replicate itself. As many as 10 million to 10 billion virions (individual viruses) are produced daily. In the first 24 h after exposure, HIV attacks or is captured by dendritic cells in the mucous membranes and skin. Within 5 days after exposure, these infected cells make their way to the lymph nodes and eventually to the peripheral blood, where viral replication becomes rapid (Lusso, 2006). CD4⁺ lymphocytes that are recruited to respond to viral antigen migrate to the lymph nodes. These become activated and then proliferate via complex interaction of cytokines released in the microenvironment of the lymph nodes. This sequence of events makes the CD4⁺ cells more susceptible to HIV infection, and it explains the generalized lymphadenopathy characteristic of the acute retroviral syndrome seen in adults and adolescents. In contrast, HIV-infected monocytes allow viral replication but resist killing. Thus, monocytes act as reservoirs of HIV and as effectors of tissue damage in organs such as the brain.

The HIV Life Cycle

HIV medicines in six drug classes stop HIV at different stages in the HIV life cycle.

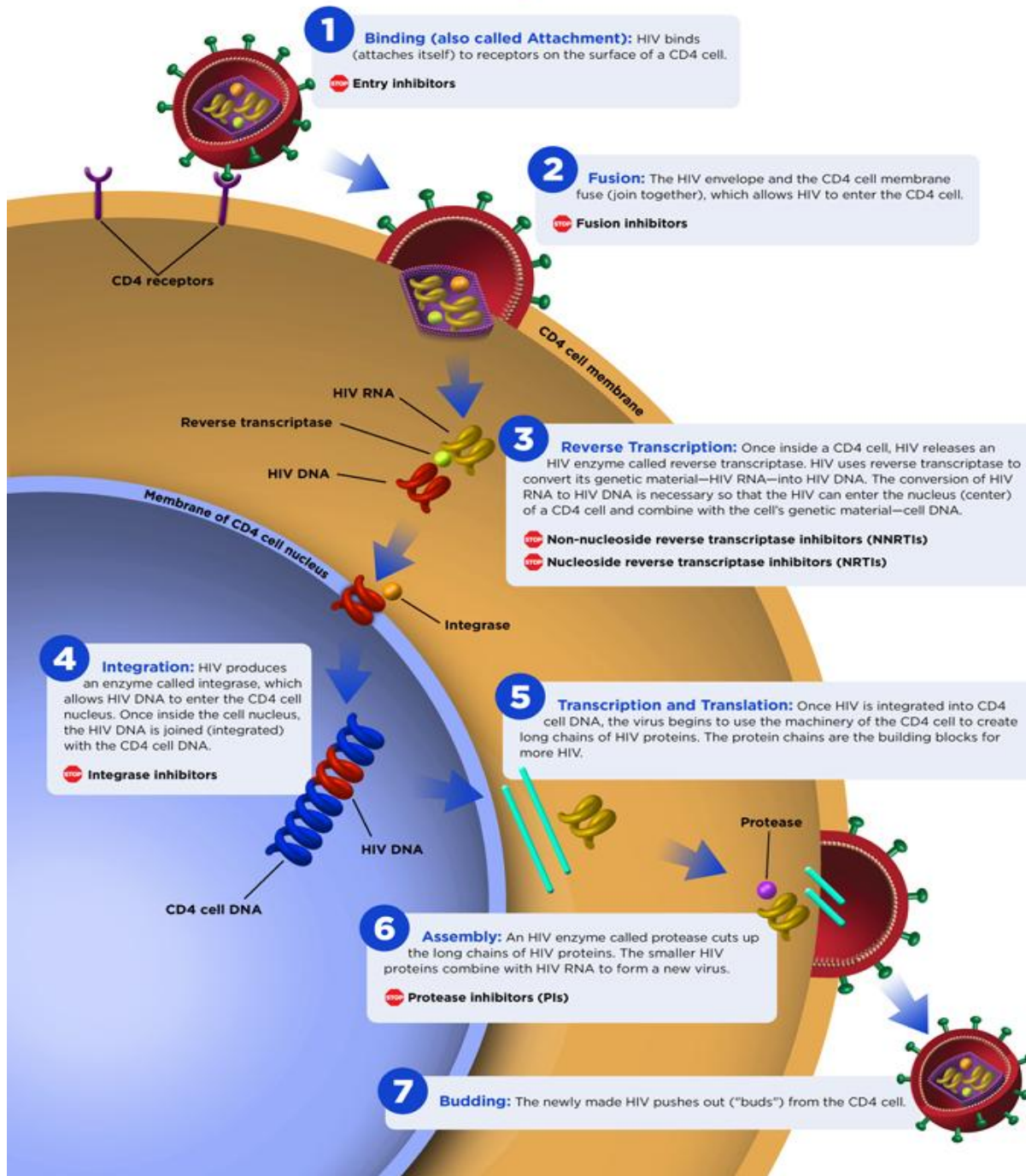


Figure 2.3: HIV Life cycle (Adapted from Hare (2009))

The first stage in life cycle of HIV is Binding and entry, the envelope proteins gp120 and gp41 bind to CD4+ cell receptors and coreceptors on the outside of CD4+ cells and macrophages. The chemokine receptors CCR5 and CXCR4 facilitate viral entry. T-cell tropic viruses require CXCR4 to bind, and macrophagic strains of the virus require CCR5. R5 is the most common virus transmitted during acute infection, and later during infection X4 is the virus that is most common. The presence of a homozygous inactive mutation of the CCR5 allele has caused resistance to infection by the R5 virus (Currie and Boon, 2003).

The joining of the proteins and the receptors and coreceptors fuses the HIV membrane with the CD4+ cell membrane, and the virus enters the CD4+ cell and macrophage. The HIV membrane and the envelope proteins remain outside of the CD4+ cell, whereas the core of the virus enters the CD4+ cell. CD4+ cell enzymes interact with the viral core and stimulate the release of viral RNA and the viral enzymes reverse transcriptase, integrase, and protease (Dadgoster *et al.*, 2006).

Next is the Reverse transcription. The HIV RNA is converted to DNA before it can be incorporated into the DNA of the CD4+ cell. This incorporation must occur for the virus to multiply. The conversion of HIV RNA to DNA is known as reverse transcription and is mediated by the HIV enzyme reverse transcriptase. The result is the production of a single strand of DNA from the viral RNA. The single strand of this new DNA then undergoes replication into double-stranded HIV DNA. Once reverse transcription has occurred, the viral DNA can enter the nucleus of the CD4+ cell. The viral enzyme integrase then inserts the viral DNA into the CD4+ cell's DNA. This process is known as integration. The CD4+ cell has now been changed into a factory used to produce more HIV (Awodu *et al.*, 2011).

Budding: The HIV proteins and viral RNA gather at the CD4 membrane to form new Viruses. During budding, the HIV envelope also acquires host membrane proteins and lipid bilayer. The newly assembled virus pushes out (buds) from the host cell. These new viruses leave the CD4 cells

containing all the components necessary to infect other cells (Rodríguez *et al.*, 2006). The new DNA, which has been formed by the integration of the viral DNA into the CD4+ cell, causes the production of messenger DNA that initiates the synthesis of HIV proteins. The HIV proteins and viral RNA, all the components needed to make a new virus, gather at the CD4+ cell membrane to form new viruses. These new viruses push through the different parts of the cell wall by budding. Many viruses can push through the wall of one CD4+ cell. These new viruses leave the CD4+ cell and contain all the components necessary to infect other CD4+ cells. **Maturation:** The last stage of the cycle is maturation process when the HIV protease enzyme cuts the long HIV proteins of the virus into smaller functional units that then reassemble to form a mature virus ready to infect other cells (Weber, 2001).

Epidemiology

HIV, the virus that causes AIDS, "Acquired Immunodeficiency Syndrome" has become one of the world's most serious health and development challenges. HIV is a leading cause of death worldwide and the number one cause of death in Africa. The first cases were reported in 1981 and today, there are approximately 35 million people currently living with HIV and tens of millions of people have died of AIDS-related causes since the beginning of the epidemic.(UNAIDS, 2014). Most people living with HIV or at risk for HIV do not have access to prevention, care, and treatment, and there is still no cure.HIV primarily affects those in their most productive years; about 40% of new infections are among those under age 25 (UNAIDS, 2013). Globally, there were 3.2 million children living with HIV in 2013, 240,000 new infections among children, and 190,000 AIDS deaths. Women represent half (50%) of all adults living with HIV worldwide. HIV is the leading cause of death among women of reproductive age. Gender inequalities, differential access to service, and sexual violence increase women's vulnerability to HIV, and women, especially younger women, are biologically more susceptible to HIV. Young people, ages 15-24, account for approximately 33% of new HIV infections (among those 15 and over).

In 2013, there were 35.0 million people living with HIV, up from 29.8 million in 2001, this is as a result of continuing new infections, people living longer with HIV, and general population growth. The global prevalence rate (the percent of people ages 15-49 who are infected) has leveled since 2001 and was 0.8% in 2013. 1.5 million people died of AIDS in 2013, a 35% decrease since 2005. Deaths have declined due in part to antiretroviral treatment (ART) scale-up. New HIV infections globally have declined by 38% since 2001. In 27 countries with sufficient quality data, new HIV infections have decreased by more than 50% and by more than 75% in 10 countries. Still, there were about 2.1 million new infections in 2013 or about 6,000 new infections per day. Although HIV testing capacity has increased over time, enabling more people to learn their HIV status, approximately half of all people with HIV are still unaware they are infected (WHO/UNAIDS/UNICEF, 2013). The scourge of HIV has been particularly devastating in Sub-Saharan Africa with almost 30 million people infected with HIV. While new cases have been reported in all regions of the world, approximately 71% are in sub-Saharan Africa making the region the highest hit. Most people living with HIV or at risk for HIV do not have access to prevention, care, and treatment, and there is still no cure (UNAIDS, 2014). HIV primarily affects those in their most productive years; about 40% of new infections are among those under age 25 (UNAIDS, 2013). Most children with HIV live in this region (91%). In some areas, young women are more heavily impacted than young men. Almost all of the region's nations have generalized HIV epidemics that is, their national HIV prevalence rate is greater than 1%. In 9 countries, 10% or more of adults are estimated to be HIV-positive. South Africa has the highest number of people living with HIV in the world (6.2 million). Swaziland has the highest prevalence rate in the world (27.4%). Recent data offer promising signs, with national HIV prevalence and/or incidence stabilizing or even declining in many countries in the region (UNAIDS, 2014).

HIV not only affects the health of individuals, it impacts households, communities, and the

development and economic growth of nations. Many of the countries hardest hit by HIV also suffer from other infectious diseases, food insecurity, and other serious problems. Despite these challenges, new global efforts have been mounted to address the epidemic, particularly in the last decade, and there are signs that the epidemic may be changing course. The number of people newly infected with HIV and the number of AIDS-related deaths have declined, contributing to the stabilization of the epidemic. In addition, the number of people with HIV receiving treatment has increased to 13.6 million as of June 2014 (UNAIDS, 2014).

Transmission

Human Immunodeficiency Virus can be isolated from virtually all body fluids of HIV-infected persons including blood, sweat, tears, saliva, semen, vaginal fluids and breast milk. The virus has been found in abundance in infected blood and semen. So far only blood, semen, vaginal fluids and breast milk have been implicated in transmission. HIV is transmitted in human body fluids by three major routes: (1) sexual intercourse through vaginal, rectal, or penile tissues; (2) direct injection with HIV-contaminated drugs, needles, syringes, blood or blood products; and (3) from HIV-infected mother to fetus in utero, through intrapartum inoculation from mother to infant or during breast-feeding. According to the CDC, HIV is not spread by tears, sweat, coughing or sneezing. Nor it is transmitted via an infected person's clothes, phone, drinking glasses, eating utensils or other objects that HIV-infected people have used that are free of blood (CDC, 2008).

Sexual Transmission Sexual transmission of HIV happens when infected semen, blood, or vaginal secretions enter the bloodstream of a partner. Although HIV can be transmitted during vaginal or oral penetration, unprotected anal sex by a male or female seems to be the most dangerous.

Worldwide, sexual transmission remains the most common mode of transmission of HIV. The virus may be effectively transmitted from an infected person to his or her sexual partner (man to

woman, man to man, or woman to woman). Transmission between woman to woman has also been reported (Tapia, 2003). The current worldwide expansion of the AIDS epidemic is primarily driven by the sexual transmission of human immunodeficiency virus type 1 (HIV-1), and its future will be determined largely by the degree to which sexual transmission can be reduced. Although sexual transmission among homosexual males is still a significant part of epidemic spread, in the most populous regions of the world, sexual transmission among heterosexuals is the dominant mode of spread (Padian *et al.*, 1997). HIV-2 is thought to be less infectious than HIV-1, although few data are available. HIV-2 infected individuals generally have a lower viral titer in peripheral blood samples than those infected with HIV-1, and incidence rates of infection appear lower in cohorts at risk for HIV-2 than among comparable populations at risk for HIV-1 (Nduati, 2000). HIV is commonly transmitted sexually by penile anal intercourse and penile vaginal intercourse and infrequently by fellatio. Vaginal intercourse can transmit HIV to either the male or the female partner, but a number of studies have shown that the risk is higher to the female partner. Studies of homosexual men have shown consistently that the receptive partner in anal intercourse is at the highest risk of HIV infection and that risk is strongly related to the number of male sexual partners (Stal-Henning *et al.*, 1999). Anal intercourse has also been shown to be a risk factor for the female partner in heterosexual studies (Quinn, 2000). Presumably, fellatio would pose the same risk to the female partner as to the receptive oral partner in male homosexual couples, but data are lacking on the risk in heterosexuals. There is a theoretic potential of transmission from cunnilingus, but no well documented cases have been reported.

Parenteral Transmission

This may occur in the following circumstances:

1. Transfusion of blood and blood-related products: Transmission of HIV-1 and some other viruses can occur following transfusion of a blood product derived from an infected person's blood and processed into a blood component (i.e., whole

blood, packed red cells, fresh frozen plasma, cryoprecipitate, and platelets). Plasma derived blood products, which are manufactured from pooled plasma can transmit HIV-1 and other viruses depending on the production process (Roth *et al.*, 1999). HIV has been transmitted through transplantation of kidney, liver, heart, pancreas, bone, and skin: all blood containing organs or highly vascular tissues.

2. Sharing of contaminated needles and syringes: Transmission of HIV among injection drug users occurs primarily through HIV infected blood contamination of injection paraphernalia, which is re-used by an uninfected injection drug user. Behaviors that increase the likelihood, frequency, and magnitude of exposure to infected blood increase the risk of infection. Among injection drug users, several demographic and behavioural characteristics are associated with greater risk of acquiring HIV. Foremost among risk factors is the sharing of needles, syringes, and other injection equipment. Sharing is a common practice among injection drug users worldwide (Halperin and Bailey, 1999).

3. Recipients of body organs/semen/other body tissues from an HIV-infected donor: HIV has been transmitted through transplantation of kidney, liver, heart, pancreas, bone, and skin: all blood containing organs or highly vascular tissues. There are no reports of HIV tissue transmission from HIV-seropositive donors of cornea, ethanol treated and lyophilized bone, fresh frozen bone without marrow, lyophilized tendon or fascia, or lyophilized and irradiated dura mater. Both intrauterine insemination and cervical insemination result in HIV transmission.

Perinatal Transmission

This is transmission from mother to child which may occur during pregnancy, at delivery or shortly after birth. The risk of transmission perinatally has been reported to be between 20% to 40%. Perinatal transmission of human immunodeficiency virus accounts for virtually all new HIV infections in children (John *et al.*, 2000) The relative contributions of in utero and intrapartum HIV transmission are unknown. One proposed scheme for differentiating these 2 modes of transmission suggests that the virus was

transmitted early or in utero if HIV is detected in the infant within the first 48 hours of live (Martinez, 2006). Late or intrapartum transmission is said to have occurred if virologic evaluations are negative during the first week of life but there is subsequent HIV detection between 7 and 90 days of age. Applying these admittedly speculative definitions to published studies suggest that 50% to 70% of HIV vertical transmission occurs intrapartum. If true, this finding has important implications for designing strategies to interrupt transmission. Breast feeding substantially increases the risk of HIV vertical transmission, therefore bottle feeding is currently recommended for all infants born to HIV infected mothers (Murray, 2000).

Other Modes of Transmission

Rare cases have been reported to the CDC of HIV transmission via acupuncture, artificial insemination, tattoo, and human bite. Most of the incidents have occurred due to the use of a used needle and the transfusion of body fluids such as blood (CDC, 2008).

Pathophysiology of HIV

Natural history of HIV infection encompasses an acute or primary infection that lasts for months, followed by a clinically latent phase that typically lasts for years and ultimately by the collapse of immune system leading that characterized AIDS (Hare, 2009).

The Acute/Primary Phase:

When one gets infected with HIV, it may take several weeks or even months for anti-HIV antibodies to appear in the circulation. This period is called the 'window period'. This is the period from initial HIV infection to the development of an antibody response detectable by standard tests (Fiebig *et al.*, 2003). During the window period, the diagnostic tests that detect an anti- HIV antibody are negative. However, this is a very important stage in HIV pathogenesis. There is a surge of viremia with plasma viral load reaching peak in two to three weeks and loss of T helper cells causing a transient drop circulating CD4 T

cells. At this stage, the most common presenting symptom is fever (Busch and Satten, 1997). Other symptoms include fatigue, headache, lymphadenopathy, rashes. Symptoms may be mild or severe and may last from a few days to several weeks, with the average of duration being 14 days (Dybul *et al.*, 2002).

The Clinically Latent Phase

After the period of acute HIV Infection during which CD4 counts and viral load change dramatically, a relative equilibrium between the viral replication and the host immune response is reached., and individuals may have little or no clinical manifestations of HIV. This time between initial infection and the development of AIDS may be long, with average of 10 years even without treatment (CDC, 2008).Despite the relative clinical latency of this phase of HIV infection, viral replication and CD4 cell turnover remain active; there is constant multiplication of virus leading to destruction of CD4 T cells. The replenishment of CD4 cells cannot keep pace with the loss of lymphocytes. As a result, there is gradual drop of CD4 T lymphocyte counts in peripheral circulation (Gustavo, 2012; Moore *et al.*, 2006)).

AIDS Stage

The gradual decrease in CD4 T lymphocyte cells below 200cells/ l or CD4 Percentage below 14%) ultimately results in loss of control over the immune response and various opportunistic infections start appearing (Mudiaya *et al.*, 2009; Walenskey *et al.*, 2009). This is the terminal stage of HIV infection. As the CD4 count drops below 200 cells/mm³, patients become vulnerable to many of the processes associated with AIDS (McMichael and Rowland-Jones, 2001). As the CD4 count drops below 50 cells/mm³, patients become increasingly at risk for the following opportunistic infections.

Malignancies -Three cancers are significantly more common among persons infected with HIV;Kaposi's sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. In addition, there is epidemiologic evidence to suggest that

cervical and anal dysplasia are associated with HIV (CDC, 2008; Gross, 2004).

FACTORS INFLUENCING DISEASE PROGRESSION

Host Factors

A number of host factors influence HIV disease progression. Individuals who acquire HIV at an older age tend to have more rapid disease progression and shorter survival times. Variation in HIV coreceptor molecules, notably CCR5, influences both HIV susceptibility and disease progression. A mutant allele of CCR5 with a 32-base-pair deletion, CCR5-delta-32, is frequent in populations of European origin (10-15% of Caucasians are heterozygous, and 1% are homozygous), and encodes a nonfunctional truncated protein that is not transported to the cell surface. Homozygotes for the delta-32 allele exhibit a strong, although not complete, resistance to HIV infection, whereas heterozygotes display nearly normal rates of infection, but delayed progression to AIDS (Kostrikis *et al.*, 1999; O'Brien *et al.*, 1997). Genetic differences in HLA alleles have also been shown to influence HIV disease susceptibility and disease progression. The class I alleles B35 and Cw4 have been associated with accelerated progression of disease, as has general HLA homozygosity (MacDonald *et al.*, 2000). Because HLA class I alleles determine which viral epitopes can be presented to CD8 cells, greater diversity of HLA (heterozygosity) in an individual may reflect greater options for effective cell-mediated immunity to HIV. Conversely, HLA B27 and B57 have been associated with long-term nonprogression of HIV disease. In particular, HLA B*5701 has been found to be highly overrepresented in long-term nonprogressors (Ali *et al.*, 2000; Jotwani *et al.*, 2012). Behavioral or psychological host factors may also influence HIV disease progression. More rapid HIV disease progression has been reported with unprotected anal intercourse, smoking, poor nutrition, and depression; however, not all studies confirm these findings. Drug use might be expected to influence HIV disease progression, but studies of that question have produced mixed results.

Additionally, differences in disease course based on the route of HIV transmission have been difficult to prove (Valdez *et al.*, 2002; Albarracin *et al.*, 2005).

Viral Factors

HIV virions infect human cells by first binding to the CD4 receptor on the cell surface. This alone is not sufficient for the virus to enter the host cell; binding to an additional coreceptor is also required. Macrophage- or M-tropic viruses preferentially infect monocytes and macrophages, using the cell surface protein CCR5 (R5) as the preferred coreceptor to enter cells, and produce a nonsyncytium-inducing (NSI) phenotype in cell culture. Conversely, thymocyte- or T-tropic viruses preferentially infect T cells, use CXCR4 (X4) as the preferred coreceptor to enter cells, and produce a syncytium-inducing (SI) phenotype in cell culture. Dual-tropic viruses, which may use either CCR5 or CXCR4 coreceptors, also exist. M-tropic viruses are frequently found in early HIV infection, and a switch to T-tropic strains in the course of disease is associated with rapid CD4 cell depletion (Biti *et al.*, 1997).

The concept of viral "fitness" refers to the pathogenicity of certain strains of HIV. HIV replicative capacity (RC) has been studied as a component of viral fitness. RC is a measure of the ability of a given virus to replicate successfully in a given environment. During the course of drug treatment, mutations arise in the HIV reverse transcriptase and protease enzymes that make the virus resistant to particular drugs, thus conferring a selective advantage to that subpopulation that arises from a resistant variant. Several of these mutations have been shown to cause a reduction in RC in the absence of drug when compared to wild-type virus. Further accumulation of mutations over time under drug selection pressure may increase the "fitness" of the drug-resistant variant by further increasing phenotypic resistance, or by increasing RC of the resistant virus (Balotta *et al.*, 1997). The role of viral fitness on individual disease progression is just beginning to be understood. Additionally, rare individuals who are infected with variant HIV strains, particularly those with a defective nef

gene product, may experience slower disease progression (Kaleebu *et al.*, 2002).

Co infections

The development of opportunistic infections during HIV disease not only indicates the degree of immunosuppression, but may also influence disease progression itself. When stratified by CD4 counts, patients with prior histories of opportunistic infections have higher mortality rates than those without prior histories of OIs. Hepatitis C coinfection is common in HIV-infected patients, present in up to 40-50% of all patients in urban setting and in 90% of intravenous drug users (Sulkowski *et al.*, 2000). HIV clearly leads to more rapid HCV disease progression; however, the effect of HCV infection on HIV progression is less clear. In a study of the Swiss HIV Cohort, HCV coinfection was associated with poorer CD4 responses to ART, development of new AIDS-defining events, and increased mortality; however, other authors have not found these associations (Greub *et al.*, 2000; Sulkowski *et al.*, 2002).

Genetic Factors

Genetic factors also play a role in susceptibility and resistance to HIV infection. The most important of these is a deletion (CCR5-32) in the major co-receptor for entry of primary HIV strains into CD4⁺ T-cells, a chemokine receptor called CCR5. Homozygotes for the deletion (~1% of Caucasians) do not express the receptor at the cell-surface, and, therefore, can only become infected with strains of HIV that are able to use other co-receptors, such as CXCR4 (Kostrikis *et al.*, 1999).

Long-Term-Nonprogressors

There are also individuals who become infected, but do not progress to AIDS. These long-term survivors, or long-term non-progressors, include individuals who have been AIDS-free as long as eighteen years after infection. A variety of factors may be responsible; for example, infection with less-virulent viruses. Some long-term non-progressors seem to have CD8 cells, which are

particularly adept at curtailing HIV infection (Kaul *et al.*, 2000). In most AIDS patients CD8 cells become less active.

This subset of individuals infected with HIV--probably <5%--remain free of symptoms, achieve good control of HIV viral replication, and maintain high CD4 counts in the absence of antiretroviral medications over many years of infection. In general, LTNPs appear to have strong cellular immune responses to a variety of HIV antigens.

Genetic variation among HIV subtypes

There are five major subtypes of HIV, designated A through E. Different subtypes predominate in different geographical areas. For example, subtype B is more common in North America. In contrast, subtype C predominates in sub-Saharan Africa. Considerable variation within a given subtype also exists. In fact, any given individual infected with HIV will harbor multiple variants of the virus. HIV makes many mistakes as it copies its viral RNA to the DNA that integrates into the host's chromosome. Because of its sloppy copying of reverse transcriptase, HIV's mutation rate is high, causing great variability. This large number of variants makes the virus more difficult to treat and hinders vaccine development (Hanke and McMichael, 2000). In addition, because of its rapid rate of evolution, even within a single individual, HIV can quickly evolve resistance to the drugs the individual is taking to combat the virus (Eaton and Kalichman, 2007).

DIAGNOSIS

The challenges of managing HIV infection include difficulties with direct detection of the virus, a prolonged asymptomatic period of infection, and decisions regarding the initiation of therapy and regimen changes in response to antiretroviral drug resistance or intolerance. All of these rely on laboratory testing to guide the clinician (Alidjinou *et al.*, 2014). A key feature of HIV infection is the prolonged clinical latency that occurs prior to significant immune deficiency. During this period (which can last several years from the time of initial infection),

the individual may exhibit few or no symptoms but is still able to spread the infection to others and may be at risk of life-threatening opportunistic infections (Colfax *et al.*, 2002). Early detection is important for minimizing those risks (Claassen *et al.*, 2012). There are specific and unique laboratory techniques that are used with HIV infection that medical providers should be aware of, in terms of availability, utility, and limitations. Diagnosis is typically made by a combination of screening and confirmatory serologic tests (Orkuma *et al.*, 2014). During therapy, it is crucial to monitor the response, both in terms of immune reconstitution and viral replication, as both have different implications for the patient and neither may be evidenced by any outward signs or symptoms. Treatment failures may be due to the development of drug resistance mutations in the virus; some mutations may result in resistance to multiple antiretroviral agents or even to entire classes of drugs (Karris *et al.*, 2012). Special tests include resistance testing by genotypic or phenotypic tests, pre-treatment tests for HLA-B*5701 in the context of abacavir, and viral tropism testing in the case of maraviroc. The laboratory can assist with all of these issues, from diagnosis to drug-resistance testing. Antibody tests are typically positive no sooner than 2 weeks after exposure, but seroconversion may take as long as several months (Fiebig *et al.*, 2003; Phillips, 2000). Thus, testing algorithms for exposed patients include baseline serology with repeat testing at 1, 3, and 6 months post exposure.

Diagnosis in newborns

Serology is not helpful in the context of diagnosing neonatal HIV infection, because maternal IgG transferred during the third trimester of pregnancy will cause positive ELISA and Western blot results in all infants born to HIV-infected mothers. In fact, this is sometimes exploited as part of newborn screening tests to detect HIV exposure.

HIV infection and cardiovascular disease

There has always been evidence that HIV itself could contribute to the development of heart

disease in the HIV infected person (Gustavo, 2012). However, the risk of cardiovascular disease increased compared with that in uninfected persons. This fact is substantially due to a higher prevalence of underlying traditional cardiovascular risk factors that are mostly host dependent. HIV may additionally contribute both directly through immune activation and inflammation, and indirectly through immunodeficiency (Akpan, 2012; Balt, 2013). A study confirmed that HIV positive people were twice as likely to suffer a heart attack than HIV negative people (Althoff and Gange, 2013). Also another study showed that a woman's risk for a heart attack tripled after she became HIV infected and a man had a 40% increase in risk after being HIV infected. So it is becoming more obvious that HIV has an impact on cardiac health. While there are many theories regarding the impact of HIV on cardiac disease risk factors, HIV medications have emerged as the biggest culprits. Protease Inhibitors have been identified as increasing cardiac risk factors such as cholesterol and triglycerides levels (Klein *et al.*, 2002; Triant *et al.*, 2007). Most recently, as mentioned above, two drugs from the Nucleoside Reverse Transcriptase Inhibitor class has been shown to increase the risk of heart attack in HIV seropositive subjects taking them. And as we have heard many times, certain factors increase the risk of cardiac disease regardless of HIV status. If a person exhibits three or more of these risk factors, he is considered to have Metabolic Syndrome (Capeau *et al.*, 2012; Grunfeld *et al.*, 2010). These risk factors include:

- central obesity (fat accumulation around the waist)
- hypertension (high blood pressure) (>130/85)
- elevated triglycerides (serum triglycerides >150)
- low HDL (<40)
- high triglycerides
- elevated fasting serum glucose (>100)

The presence of metabolic syndrome increases the risk of heart disease in people with or without HIV. But in HIV, metabolic syndrome takes on some unique characteristics. For instance, altered

fat distribution is more exaggerated in HIV. Fat is redistributed to the abdomen, neck and back from the face and extremities (Aristoteli, 2006; Young *et al.*, 2005). HIV medications can significantly alter cholesterol and triglyceride levels. Finally, blood sugar changes and hypertension are associated with HIV above and beyond what we see in the HIV negative population. Because of this fact, HIV specialists have become very aggressive in their management of metabolic syndrome.

HAART and cardiovascular disease

ART cause hyperlipidemia or the lipodystrophy syndrome, which is manifested by peripheral fat wasting (lipoatrophy) and visceral fat accumulation (lipohypertrophy). This is a class effect of the PIs, and also occurs frequently with the NRTIs, in particular stavudine (Jun *et al.*, 2010). The NRTIs are also associated with hepatic steatosis related to mitochondrial toxicity (dysfunction and reduction of mitochondria), most commonly with stavudine and didanosine. Of the NRTIs, stavudine mainly causes increased triglycerides (TG), but may also increase low density lipoprotein cholesterol (LDL-C) and total cholesterol (TC). Of the NNRTIs, efavirenz is more likely to cause hyperlipidemia than nevirapine. All of the PIs except atazanavir have been associated with hyperlipidemia (Johnson *et al.*, 2004). PIs, and in particular ritonavir-boosted PIs, cause elevations of LDL, TC and TGs and a decrease in high density lipoprotein cholesterol (HDL-C). PIs suppress the breakdown of transcription factors such as nuclear sterol regulatory element binding proteins (nSREBPs), which are important in lipid homeostasis (Aukrust *et al.*, 2000; Durand *et al.*, 2011). This leads to accumulation of nSREBP in the liver, causing increased cholesterol and fatty acid synthesis, and reduced triglyceride storage, leading to increased circulating lipids, and in the tissues, causing lipodystrophy and insulin resistance. PIs also inhibit the breakdown of apolipoprotein B *via* binding to a region homologous to HIV-1 protease, thereby causing excess production and circulation of triglyceride-rich lipoproteins (Beerasconi *et al.*, 2001; Rhew *et al.*, 2003). The inhibition of cytochrome P450, in particular by

ritonavir, may also disrupt fat metabolism by inhibiting the conversion of retinoic acid to cis-9-retinoic acid, which results in reduced stimulation of the retinoic X receptor (RXR). This in turn prevents adipocyte differentiation and increases adipocyte apoptosis, leading to hyperlipidemia (Boccaro *et al.*, 2013; Mu *et al.*, 2007). PIs may also bind to HIV-1 protease homologous regions on two proteins important for lipid metabolism, cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low-density lipoprotein-receptor-related protein (LRP). CRABP-1 prevents binding with retinoic acid and RXR action just as cytochrome P450 does, resulting in hyperlipidemia. LRP is responsible for chylomicron clearance in the liver, and for breakdown of triglycerides in the circulation. Therefore PI binding to LRP also contributes to hyperlipidemia (Lo *et al.*, 2008; Riddler *et al.*, 2005).

The metabolic side effects of ARVs have been some of the most difficult to manage. The metabolic syndrome, comprised of abdominal obesity, hyperglycemia, dyslipidemia, and hypertension, is associated with PI therapy (Brown *et al.*, 2010; Nguemaim *et al.*, 2010). Use of highly active antiretroviral therapy (HAART) is associated with the development of traditional cardiovascular risk factors, including dyslipidemia and insulin resistance (Lo and Plutzky, 2012). Recent data also suggests that endothelial dysfunction, impaired fibrinolysis, and excess inflammation may contribute to increased cardiovascular risk in the HIV-positive population. Surrogate markers such as C-reactive protein (CRP), tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1) are increased in the HIV-positive population in association with metabolic abnormalities and altered fat distribution (Althoff and Gange, 2013). Carotid intimal-medial thickness (IMT) and coronary calcification assessments suggest increased atherosclerotic disease among certain HIV-positive individuals. Finally, recent studies of large numbers of HIV-positive subjects have documented increased cardiovascular risk using hard endpoints such as myocardial infarction rates. This review will consider the pathogenesis, prevalence, and

treatment of cardiovascular risk factors in the HIV-positive population. Pharmacologic strategies for dyslipidemia and abnormal glucose homeostasis will be reviewed in conjunction with non-drug strategies for disease prevention (Lo *et al.*, 2008; Riddler *et al.*, 2003). Altered lipid metabolism is known to occur in association with HIV disease itself. HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and total cholesterol (TC) levels are reduced, while triglyceride (TG) levels are increased in HIV-positive patients. Early data suggest that circulating TG levels may be elevated from increased hepatic very low-density lipoprotein (VLDL) production and reduced clearance. Cytokines, such as interferon alpha, may play a role in the abnormal lipid homeostasis seen in HIV-positive patients (Kwong *et al.*, 2006; Nguemaim *et al.*, 2010).

Protease inhibitor (PI) use has been linked to further abnormalities in the serum lipid profile in HIV-positive patients. Increased TC, TG rich VLDL, and LDL-C are seen in PI-treated patients relative to PI-naive, HIV-positive individuals. Data from prospective cohort studies report new-onset hypercholesterolemia and hypertriglyceridemia after 5 years of HAART therapy in 24 and 19% of subjects, respectively (Stanley *et al.*, 2012). Abnormalities in glucose homeostasis are common among HIV-positive individuals treated with HAART. HIV-positive individuals may be diabetic, or more commonly, demonstrate impaired glucose tolerance and insulin resistance. Use of the WHO definitions (fasting glucose > 126 mg/dl defines diabetes, and fasting glucose > 110 mg/dl impaired fasting glycemia) is recommended to characterize glucose abnormalities in the HIV-positive population. The glucose response to a standard 75 g glucose challenge may also be useful to identify individuals with impaired glucose tolerance. Insulin resistance is common during HAART therapy, and may manifest as fasting hyperinsulinemia or reduced glucose disposal after an oral or IV glucose challenge; fasting glucose need not be elevated (Brown *et al.*, 2010; Murata *et al.*, 2000). Mechanisms of insulin resistance in the HIV-positive population are not known, but may relate to altered nutrient metabolism, changes in body composition, and/or

direct effects of antiviral agents. Preliminary data include the demonstration of altered lipolysis and increased serum free fatty acids in HIV-positive individuals (Koster *et al.*, 2003). Excess free fatty acids in the circulation may reduce insulin sensitivity through inappropriate lipid storage in muscle and liver, resulting in impaired glucose utilization and insulin-mediated inhibition of glycogenolysis and gluconeogenesis (Grunfeld *et al.*, 2010). PI therapy is associated with higher rates of diabetes mellitus, impaired glucose tolerance, and hyperinsulinemia among HIV-positive individuals. This effect is not class specific, and newer PI drugs such as atazanavir appear less likely to affect glucose homeostasis. A direct link between ARV medication and abnormal glucose homeostasis is substantiated by physiologically rigorous evaluation of indinavir, and more recently, lopinavir/ritonavir in HIV-negative individuals. The mechanisms behind PI-induced insulin resistance are complex and multifactorial. Initial studies suggested an effect on Glut-4-mediated glucose transport. Islet cell dysfunction and dysregulated hepatic glucose production may complicate glucose homeostasis further in HIV-positive individuals receiving HAART (Scherzer *et al.*, 2008). Preliminary data suggest that PIs may inhibit the processing of insulin from pro-insulin. Mitochondrial toxicity could contribute to the detrimental effect of NRTIs on tissue insulin sensitivity either through impaired oxidative phosphorylation and excess lipid accumulation in liver or muscle or via a reduction in the absolute or relative amounts of subcutaneous fat (De Luca *et al.*, 2012). HIV-positive individuals receiving HAART commonly manifest evidence of fat redistribution, characterized by loss of subcutaneous extremity fat, relative preservation of fat in the trunk, and an increased waist-to-hip ratio (WHR). It is well established that increased truncal adiposity confers heightened risk of cardiovascular complications in the general population. Intra-abdominal fat delivers excess free fatty acids directly into the portal blood system and secretes cytokines and other factors that contribute to insulin resistance, impaired fibrinolysis, and endothelial dysfunction (Huang-Doran *et al.*, 2010; Wohl *et al.*, 2008)). Significant evidence suggests that markers of impaired fibrinolysis are

increased in HIV in association with insulin resistance and various altered metabolic pathways. The anti-fibrinolytic factor PAI-1 is increased in association with insulin-resistance and correlates with risk of myocardial infarction. Similarly, increased tPA is associated with myocardial infarction and stroke in HIV-negative individuals. Increased homocysteine concentrations also correlate with excess cardiovascular risk (Lake *et al.*, 2011). Among HIV-positive subjects treated with HAART, homocysteine, tPA and PAI-1 are increased. Metformin treatment decreased serum tPA and PAI-1 activity in patients with HIV lipodystrophy, in association with improvement in insulin sensitivity (Althoff *et al.*, 2010).

Pathophysiology of HIV-associated cardiovascular disease

Chronic inflammation, hypercoagulability and platelet activation all contribute to endothelial dysfunction, and are a probable link between HIV and cardiovascular disease (Kamin and Grinspoon, 2005). HIV influences endothelial function *via* activated monocytes and resultant cytokine secretion, and *via* a direct effect of the secreted HIV proteins *tat* and gp120. A simple measure of the chronic inflammation in HIV-infected patients is the higher levels of high sensitivity C-reactive protein (CRP) found in HIV-infected patients compared to control subjects, indicating a higher risk for cardiovascular events (Hsue and Waters, 2005). Other inflammatory markers such as interleukins are also elevated in HIV infection. Endothelial markers are increased as well, including soluble vascular cell adhesion molecule (sVCAM-1), soluble intercellular adhesion molecule (sICAM-1), and von Willebrand factor (vWF) (Wolf *et al.*, 2002). These markers indicate chronic endothelial activation and subsequent endothelial dysfunction, which may trigger inflammation and a hypercoagulable state. Endothelial activation also triggers platelet activation, which can upregulate adhesion molecules. Much is known about the direct effects of HIV on endothelial function. Nitric oxide (NO) is a mediator of endothelial dysfunction in HIV infection (Moncada and Higgs, 1993). NO is produced in

excess because of reduced expression of endothelial NO synthase (eNOS) and the resultant increased expression of an inducible NO synthase (iNOS) (Van Leuven *et al.*, 2008). Then excess NO reacts with oxygen radicals to produce peroxynitrite, which then causes oxidative damage to the vascular endothelium, and decreased flow mediated dilation (Jacobson *et al.*, 2004; Torre, 2006). The HIV transactivator of viral replication (*tat*) protein has been found to significantly decrease eNOS mRNA and thus impair vasorelaxation in porcine coronary arteries (Paladugu *et al.*, 2003). The HIV surface protein gp120 (envelope glycoprotein) also stimulates NO production in activated macrophages, and directly activates endothelial cells resulting in increased adhesion of leukocytes to the endothelium, causing endothelial damage (Mu *et al.*, 2007). Clinical evidence of a link between NO and cardiovascular disease was found in a study of HIV-associated cardiomyopathy. Levels of TNF- α and iNOS were significantly higher in HIV-positive individuals with cardiomyopathy on endomyocardial biopsy than in HIV-negative cardiomyopathy patients (Currie *et al.*, 2003). The HIV *tat* protein activates mononuclear cells to secrete cytokines IL-6, IL-8, and TNF- α , which activate endothelial cells and enhances leukocyte adhesion. Both IL-6 and IL-8 are increased in HIV-infected patients and increased levels are correlated with HIV viral load as well as Von Willebrand Factor (vWF), and tissue-type plasminogen activator (De Larranaga *et al.*, 2003). HIV *tat* protein further activates endothelial cells by increasing expression of adhesion molecules that enhance leukocyte adhesion to endothelium. ICAM and VCAM are induced by *tat* in vascular endothelial cells *in vitro*. ICAM and VCAM levels are increased in HIV-infected patients, and decrease with ARV treatment (Wolf *et al.*, 2002). Other effects of HIV infection include increases in IFN- γ , which has been associated with hypertriglyceridemia. HIV has also been found to lower HDL-C and increase TG; and during progression to AIDS, LDL-C decreases (El-Sadr *et al.*, 2005). Adhesion molecules such as E-selectin and Von Willebrand Factor, which promote the endothelial adhesion of platelets, are also increased in HIV infection. Platelet activation is increased *via* vWF in HIV

infection, contributing to an increased incidence of thromboembolic events (Aukrust *et al.*, 2000). Activated coagulation factors and reduced anticoagulants also are important in contributing to thromboembolic events in HIV infection. Activation of coagulation mechanisms may occur through endothelial activation and inflammation. The HIV envelope protein gp120 has been shown *in vitro* to activate smooth muscle cells *via* the chemokine receptors CXCR4 and CCR5, and thus to cause them to express tissue factor (Scherzer *et al.*, 2011). Tissue factor, in turn, initiates the coagulation cascade leading to thrombosis. Coagulation abnormalities in HIV include decreases of protein S levels by 73%; increased levels of anticardiolipin antibodies and lupus anticoagulant, and decreased levels of antithrombin are also seen (Hsue and Waters, 2005). Finally, HIV-induced apoptosis is another mechanism of endothelial injury. HIV Gp120-induced apoptosis has been implicated in lung endothelial injury contributing to pulmonary hypertension, and HIV *tat* has been associated with endothelial apoptosis *in vitro* (Mu *et al.*, 2007). Taken together, it is clear that HIV abnormally affects many aspects of cardiovascular physiology.

Many studies have evaluated the effect of HIV on endothelial function, using endothelial function as a proxy for cardiovascular risk. Endothelium-dependent vasodilatation, as measured by flow-mediated dilation (FMD) of the brachial artery, was significantly diminished in 75 HIV seropositive subjects compared to HIV-uninfected controls in a multivariate analysis study (Triant *et al.*, 2007). In this study, smoking, male sex, and obesity were also independently linked to decreased FMD, which is a reminder of the association of smoking and obesity with endothelial dysfunction, and the importance of addressing these risk factors in HIV-infected patients. PI therapy was not an independent risk factor for endothelial dysfunction. In a separate study, 22 HIV-infected patients taking PIs did have impaired FMD compared to 15 HIV-infected patients not taking PI therapy. The group taking PIs had significantly higher levels of chylomicron, VLDL, LDL, and HDL cholesterol levels, which likely contributed to the endothelial dysfunction seen (Stein *et al.*, 2001). A study in

rats examined whether the NRTI zidovudine (AZT) causes endothelial dysfunction. AZT alone, and AZT plus indinavir both decreased vessel relaxation (Jiang *et al.*, 2006). Therefore NRTIs and PIs may both play a role in the endothelial dysfunction seen in HIV-infected patients. However, since ARVs reduce the endothelial activation caused by uncontrolled HIV infection, their overall effect on endothelial function is still an area of active research and controversy.

Cardiovascular epidemiology of HIV infection

A START (Short Term Antiretroviral Therapy) study carried out at Asokoro District Hospital Abuja Nigeria showed that ART plays a major role in promoting arterial and venous thrombosis among HIV-infected persons as early as 3 months into the treatment. Premature coronary artery pathology has been reported among HIV-positive individuals. Autopsy studies first suggested an association between vascular endothelial pathology and HIV (Passalaris *et al.*, 2000). Reporting of clinically evident coronary artery disease (CAD) has increased since the introduction of PIs in 1996. HIV seropositive subjects have higher rates of MI than non-HIV seropositive subjects, 11.13 versus 6.98 per 1000 person-years in a recent US study. A Danish study found that HIV seropositive subjects receiving highly active antiretroviral therapy (HAART) were more likely to be hospitalized with ischemic heart disease than HIV-uninfected controls. Similarly, a Kaiser Permanente study found a higher rate of cardiovascular events in HIV seropositive subjects who were not receiving ARV therapy compared to HIV-uninfected controls (Althoff and Gange, 2013; Klein *et al.*, 2002). Several large studies have compared rates of CAD among HIV-positive patients who are taking PIs compared to those who are not. The HIV Outpatient Study (HOPS) found increased frequency of MIs after the introduction of PIs and a hazard ratio of 7.13 by univariate analysis for myocardial infarction in those who used PIs. The hazard ratio on multivariate analysis was 6.51 but did not reach significance. Corroborating this finding was an Italian study that found patients who received PIs had an annual coronary event

rate of 5.1/1000 while those who received NNRTIs had an event rate of 0.4/1000 (Babaro,2005). Another study using data from the HOPS study and other outpatient clinics found event rates of 9.8/1000 and 6.5/1000 for patients who had and had not been exposed to PIs, respectively ($p=0.0008$). A study of the French Hospital Database found an increase in the relative risk of MI with increasing length of time on PI therapy (Mary-Krause *et al.*, 2003). In a follow-up study combining data from HOPS and the Athena national cohort in the Netherlands, an increased risk of MI was found in those on PI therapy (hazard ratio 1.19, $P= 0.04$), but not on NNRTI therapy (Kwong *et al.*, 2006). However, a reduction in a combined endpoint of death and atherosclerotic events of patients on NNRTI or PI-based therapy compared to patients not on therapy was found, underscoring the importance and positive benefits of HAART.

The Data Collection on Adverse events of Anti HIV Drugs (D:A:D) study also found that the incidence of MI increased with length of time on HAART, with an adjusted relative risk of 1.26 (26%) per year of exposure, though the absolute incidence of cardiac events was low at 3.5 per 1000 person-years. A subsequent analysis of the D:A:D study separating the effect of PIs versus NNRTIs found that patients taking PIs had an increased relative risk of MI of 16% per year, while the risk of MI for patients taking NNRTIs was not significantly increased (Friis-Moller *et al.*, 2007). When adjusted for lipid levels, diabetes mellitus, and hypertension, the relative risk of MI per year was increased only 10%, suggesting that lipid changes accounted for some, but not all, of the risk associated with PI therapy. Another recent finding from the D:A:D study is that abacavir and didanosine were independent risk factors for MI. Recent use of abacavir or didanosine, regardless of duration of use, was associated with a 90% and 49% increased risk of MI, respectively. Zidovudine, stavudine, and lamivudine were not associated with increased risk of MI (Ding *et al.*, 2012). However, it is important to remember that the increase in absolute risk attributable to PIs is small. It should be emphasized that the significance of an increased risk of CAD is dependent on the

patient's underlying cardiac risk factors. Since risk of CAD is increased by a factor of 1.16 per year of PI therapy, or a doubling of risk over a 5-year period, PIs will confer minimal increased risk to someone with a low starting risk of CAD (Kaplan *et al.*, 2007). The importance of addressing underlying cardiac risk factors, such as tobacco use, must be emphasized. Some of the effects of PI therapy, such as dyslipidemia and insulin resistance, can be medically managed to further reduce CV event risk.

Other studies have reported a decrease in CV risk in patients receiving ARV therapy. HAART appeared to decrease the risk of cardiac disease in the Strategies for Management of Antiretroviral Therapy (SMART) study. Patients in the ARV-sparing arm had an increased rate of cardiac events compared to those who remained on HAART (El-Sadr *et al.*, 2006). The increased rate of cardiac events could be related to the increase in inflammation caused by rising HIV viral loads in patients who stopped HAART. A recent study looked at this possibility, and found significantly increased levels of IL-6 (30% versus 5%) and D-dimer (16% versus 0%) in patients who discontinued HAART compared to those who continued HAART (Kuller, 2008). These increased levels of IL-6 and D-dimer were associated with cardiovascular events. A similar treatment interruption study found increased sVCAM, adiponectin, and IL-10 in the patients who had a treatment interruption versus those who stayed on ARV therapy (Calmy *et al.*, 2008). Another treatment interruption study found that increases in viral load correlated with increases in sVCAM (Papasavvas *et al.*, 2008). Corroborating the beneficial effects of HAART on cardiovascular risk, a large retrospective U.S. Department of Veterans Affairs (VA) study found that the admission rate for cardiovascular and cerebrovascular disease decreased from 1.7 to 0.9 per 100 patient-years from 1995 to 2001, during the time that HAART with ritonavir-boosted protease inhibitors became widely used. No association was found between cardiovascular events and the use of PIs, NNRTIs, or NRTIs (Boccaro *et al.*, 2013; Bozzette *et al.*, 2003). The mean follow-up time was 15 months, and the mean time on PIs was 16 months, so this study

may speak more to the short-term benefits of ARV treatment rather than the long term cardiovascular effects of HAART. Overall, these data on the incidence of CAD and MI in HIV-infected individuals support an initial decrease in cardiac risk with the use of ARV therapy, related to a reduction in inflammation and endothelial dysfunction caused by HIV. They do point to an increased cardiovascular risk in those on PI-based therapy, which increases with time spent on therapy.

HIV and HAART have also been associated with increased carotid artery intima-media thickening, which is used as a surrogate for cardiovascular risk. Baseline intima-media thickness (IMT) is higher in patients with HIV infection than those without, and progresses at a faster rate (Hsue and Waters, 2005). Increased IMT is associated with classic cardiovascular risk factors, such as older age, higher LDL cholesterol, smoking pack-years, and hypertension. ARV therapy has also been implicated. Along with PI exposure, lower CD4 count and genetic polymorphisms are also associated with progression of IMT.

Conclusion

Human immunodeficiency virus (HIV) is a major public health issue in Nigeria and needs more research to come up with the cure so as to improve the health and economy of the World. There is proved strong association of HIV and cardiovascular disease through chronic inflammation, hypercoagulability and platelet activation which affects the endothelial function. The drugs used for the treatment of HIV infection contribute immensely to the cardiovascular disease experienced by the patients especially protease inhibitor.

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