Review article

HIV Infection and Therapeutic Interventions: Review on HIV Infection Biology, Highly Active Antiretroviral Therapy (HAARTs), Hepatotoxicity, Nephrotoxicity and Dyslipidemia.

Abstract.

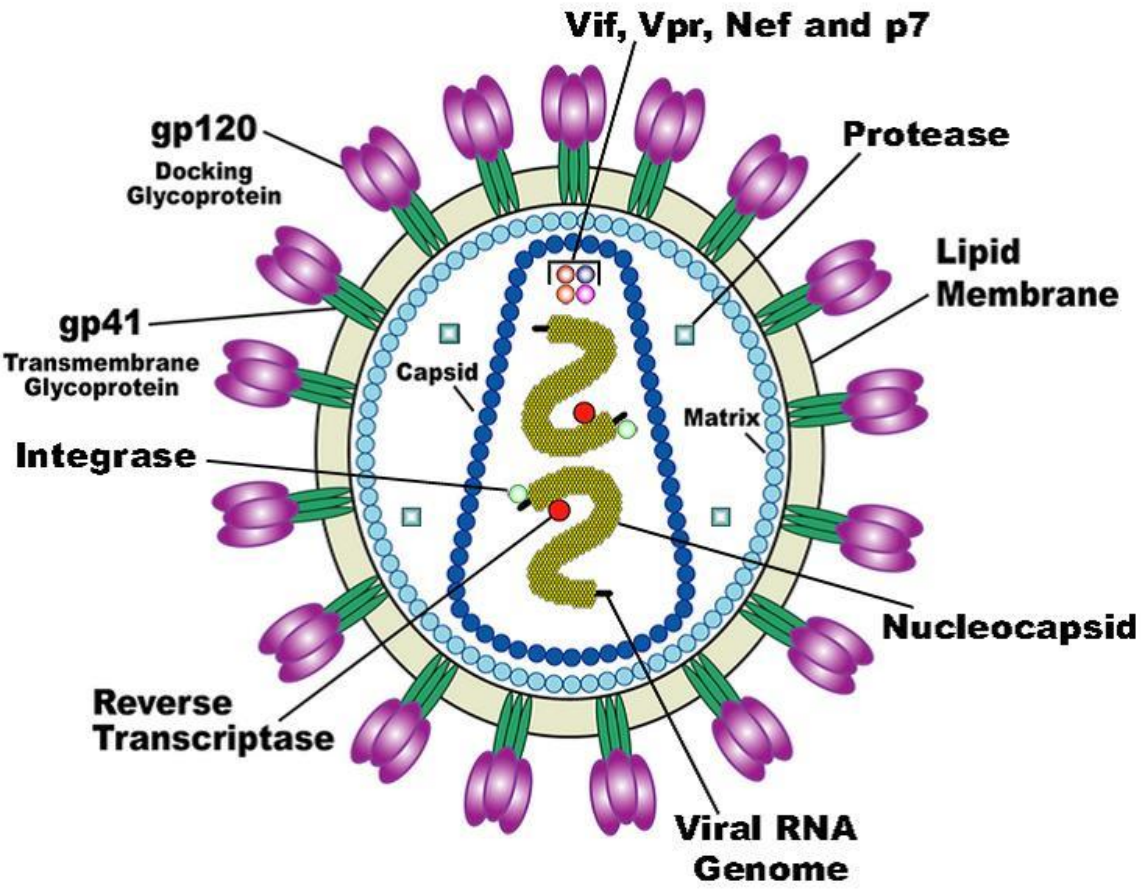
Three and half decades following the identification of HIV, the disease remains a global health grave concern as people get infected with the virus which has no cure coupled with the unavailability of vaccines. The discovery of some drugs have classified the disease into a chronic disease category. These drugs have dramatically reduced the high morbidity and mortality associated with HIV/AIDS. However, the disease has become a double-edged saw as both sides have their negative implications thus, the virus suppressing the immune system and the drugs which are intended for treatment induce pathologies in some major organs. This paper summarized the biology behind HIV infection, the therapeutic intervention and the effects of the therapeutic intervention on the liver, kidney and lipid metabolism.

1.0 Introduction

Since the beginning of the epidemic, more than 70 million people have been infected with HIV and about 35 million people have lost their lives due to HIV. Globally, 36.7 million (30.8-42.9 million) people were living with HIV at the end of 2016 [1]. An estimated 0.8 % (0.7-0.9 %) of adults aged 15-49 years globally are living with the disease although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan African remains most severely affected, with nearly 1 in every 25 adults (4.2 %) living with HIV and accounting for nearly two-thirds of the people living with HIV globally [1]

HIV structure

A diagrammatic representation of HIV



Source: US National Institute of Health (2005)

The HIV is well known to have a rough circular shape but its viral envelop may have varying shapes, from spherical to oval or even sometimes having an irregular outlines. At maturity, the virus comprises of a bar-shaped electron dense core which enclose the viral genome. The viral genome consist of 9200 nucleotides base pair of short strands of ribonucleic acid (RNA) surrounded by enzyme reverse transcriptase, protease, ribonuclease, and integrase, all encased in an outer lipid envelop. Projections on the surface of the outer lipid envelop contain

gp120 which help the virus to bind to the target cell. When observed under an electronic microscope, a budding virus particle of 90-1009 nanometers in diameter is seen in the plasma membrane of an infected CD4+ lymphocyte [2, 3].

HIV-1 and HIV-2 are the two serotypes of HIV with the same mode of transmission. HIV-1 serotype is more common worldwide than HIV-2 strains, with West Africa recording the highest number of HIV-2 serotypes. HIV-1 serotype can be classified into Group M which is the major group and Group O; the catch all category. Group M are dotted throughout the world and have 10 subtypes (A-J) of viruses. The subtypes are distributed as follows: subtypes A and D in Sub-Sahara Africa region; subtype C in South Africa; subtype E in Central Africa Republic with subtype B commonly found in industrialized world but less common in Africa. HIV infection is mostly transmitted through sexual intercourse whether homosexual or heterosexual engagement from the body fluid of the infected individual to his/her partner, mothers having the virus can also transmit it to their babies during pregnancy, at the point of delivery or through breast feeding thus; Mother-To-Child Transmission (MTCT) and intravenous drug users can also be infected with the virus when they administer injections using a single infected syringe [4].

2.0 Replication and Pathogenesis of HIV

The absence of deoxyribonucleic acid (DNA) in Retroviruses makes it impossible for it to make a copy of itself outside the infected host cells. Pathogenesis in HIV infected person may include a lot of factors but not limited to virus life cycle, cellular environment of the host, and the viral load of the infected individual. The virus upon gaining access into the body attaches itself to the host cells through surface CD4 receptor. After which it empties its viral genome by fusion or endocytosis into the host cells. It then integrates its viral genome into the DNA of the host and then makes similar copies thereof. The rate of infection may depend on the

number of HIV virion in the infected individual and the number of cells having the appropriate CD4 receptors [2, 4]

The CD4 cells are the main target of the HIV hence they invade the CD4 cells and destroy them. The immune system becomes weaker as more CD4 cells are being destroyed by the fast replicating HIV virus. Reduction in CD 4 T cells level are as a result of cytotoxic effect of CD8 lymphocyte, programmed cell death of infected cells (apoptosis) and the viral attack. The virus may also target immune cells like macrophages and dendritic cells [4, 5]. Pathogenesis in HIV infection primarily begins with the attack of the virus on activated CCR5+CD4+ T cells [5]. The lymph node harbours milliard of these type of lymphocytes and becomes inflamed with increased adhesive molecule upon incessant attacks from the virus. This may result in lymphadenopathy syndrome at the early stage of HIV infection. Similar attack happens at mucosal membrane of the gastrointestinal tract which also harbours a lot of activated CD4+ memory T cells with HIV co-receptor CCR5 [6,7]. As the infection progress, a lot of memory CD4+ T cells in the lymphoid and circulation site are discriminately destroyed which completely eliminates the presence of naive and memory phenotype CD4+ T cells [8]. The rate of depletion of CD4+ T cells in the peripheral blood is much slower as compared to the excessive deterioration at the mucosal sites. Nevertheless, the depletion observed in the peripheral blood gives us a clue on the progress of HIV pathogenesis [4]. The high extent of depletion of CD4+ T cells both in the mucosal sites and the peripheral blood circulation are accompanied with a rise of systemic immune activation [9-12] which results in high levels of serum inflammatory cytokines. When CD4+ T cells level drastically fall below normal, the immune system's ability to fight the HIV virus becomes lessens and that exposes the body to other opportunistic infections like Tuberculosis, shingles, oral or vaginal thrush, herpes simplex virus, and Kaposi sarcoma [12]. Certain stage of infection records complete absence CD4+ T cells both in the lymphoid and circulation sites. At this stage the infected

HIV individual starts experiencing Acquired Immunodeficiency syndrome (AIDS) condition [13]. AIDS ushers the gradual breakdown of the immune status as a result of the reduced level of CD4 T cell and high levels of inflammatory cytokines which suppresses other immune cells from replenishing lost ones. Contrarily to CD4+ T cell, CD8+ T-cell rather increase in their numbers due to the expansion of memory CD8+ T cells. Expansion of CD8+ T cell may reduce at the later stage of HIV infection [14]. Although naïve CD8+ T cell may decrease during the beginning of HIV infection, absolute count of CD8 T cells only decline when HIV disease progresses [4, 8, 12].

3.0 Therapeutic Interventions

The discovery of novel vaccines and drugs to prevent and treat HIV infection completely has been a great challenge. Advanced immunological principles have been employed over the years but all remain futile. The introduction of the highly active antiretroviral therapy (HAART) has reduced morbidity and mortality among people living with HIV/AIDS but does not present a total cure of the infection. The use of antiretroviral drugs is noted to drastically reduce viral load in the plasma and help the immune system to progressively improve on it defence mechanism [4, 12]. Patients with low basal viral load [15], genetic factors, younger age [16, 17], and the small percentage of naive cells [18] have a greater chance of redeeming or appreciating their CD4 T-cell levels when initiated on HAART. Conversely complications like residual viral replication [19], altered thymic function [20], older age [21], immune activation [22], apoptosis, and viral co-infections [23] may hinder CD4 T cell restoration even when placed on HAART. Although ART acts in reducing T cell activation in HIV patient, it has been noted to increase in many HIV patients who had many years been on ART with minimal sign of CD4 recovery [18, 22, 24, 25]. Such patient with suppressed viremia but low level of CD4+ T-cells have high levels of pro-inflammatory cytokine [26] and independently predicts cardiovascular disease and mortality [27]. The

HAARTs can be classified into five groups. These include the Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Entry/Fusion Inhibitors and Integrase Inhibitors. The net effect of these classes of drugs is to suppress the virus to enable the immune system perform its superintendent role for uncompromised health of the individual.

3.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs): These are the first class of antiretroviral drugs. They are also referred to as "Nukes." These classes of drugs act by interfering with the reproductive process of the HIV virus. The NRTI's present themselves as one of the essential building block of the viral DNA. As a result, the viral reverse transcriptase (the enzyme responsible for the conversion of viral RNA to DNA) fails to make new copies of itself [28]. This impedes the viral replication process. Drugs belonging to this class include Ziagen (Abacavir), Viread (tenofovir disoproxil fumarate), Retrovir (Zidovudine), Zerit (Stavudine), Emtriva (emtricitabine), Epivir (lamivudine).These drugs may be combined into a single tablet such as Combivir (Zidovudine+lamivudine), Descovy (emtricitabine+tenofovir alafenamide), Epzicom (abacavir+lamivudine), Trizivir (abacavir+zidovudine+lamivudine), Truvada (tenofovir disoproxil fumarate+emtricitabine), The nucleoside analogues need to undergo phosphorylation to become active in the body. However, the nucleotide analogues (Viread) are already chemically and physiologically active hence they bypass this stage of biotransformation.

3.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): These are also referred to as "non-nukes." NNRTIs prevent the virus from replicating its own DNA by directly attaching themselves to the reverse transcriptase enzyme thereby preventing the conversion of the viral RNA to DNA. In effect, the HIV's genetic material cannot be incorporated into the healthy genetic machinery of the CD4 cells, preventing the production of new viruses [28]. Drugs belonging to this class include Efavirenz (which is available as a genetic drug),

Etravirine, Nevirapine, Rilpivirine. Viral resistance to nevirapine is likely to cause resistance to efavirenz and possibly rilpivirine

3.3 Protease Inhibitors (PIs): As the name implies it inhibits/blocks protease from effectively incising the long strand of viral genetic material into short functional units. While HIV can still replicate in the presence of protease inhibitors, the resulting virions are immature and lack the ability to infect new cells. Amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir are drugs belonging to this group. These drugs undergo biotransformation in the liver mediated by liver enzymes hence their bioavailability could be affected in patients with severe liver dysfunction.

3.4 Entry/Fusion Inhibitors: The main cascade of events during viral entry include the attachment of the viral gp120 to the CD4 T cell receptor, the binding of the gp120 to CCR5 or CxCR4 co-receptors and the fusion of the viral and cellular membranes [29]. This class of drugs blocks the attachment of the HIV gp120 to either CD4 T cell or the CCR5/CXCR4 co-receptors [29]. In so doing prevents the virus from infecting other cells. Enfuvirtide is the first clinically accepted entry inhibitor [29, 30].

3.5 Integrase Inhibitors: Integrase as the name implies is the viral enzyme that aids the virus to effectively combine its genetic material with the host DNA (DNA of T cells). This then enables the virus to control the genetic machinery of the T cells. This class of drug therefore blocks the integrase enzyme thereby preventing the virus from incorporating its genome into the host DNA. This terminates the replicative ability of the virus. The integrase inhibitors currently in clinical use includes raltegravir, dolutegravir and elvitegravir. Integrase inhibitors are often used as the initial treatment for HIV infections but are more preferably used with combination of other drugs. Example Genvoya (elvitegravir+emtricitabine+ tenofovir

alafenamide fumarate+cobicistat), Triumeq (dolutagravir+abacavir+lamivudine), Juluca (dolutegravir+rilpivirine), Stribild (elvitegravir+emtricitabine+tenofovir disoproxil fumarate+cobicistat).

The use of HAART in the treatment of HIV has been associated with some pathologies notwithstanding the fact that it has reduced morbidity and mortality associated with HIV/AIDS. The liver, kidney, pancreas, heart and some other major organs get destroyed following the infection and therapeutic intervention. Hepatotoxicity in people living with HIV/AIDS coupled with Hepatitis C and/or Hepatitis surface antigen infection lead to the withdrawal of treatment [31].

4.0 The Liver and its associated HIV and HAART Pathologies

The liver is the largest functional internal organ and weighs about three pounds in adults located in the upper right-hand part of the abdomen, below the ribs. The liver carries out about 200 functions including Storage of nutrients, breakdown of erythrocytes, bile secretion, synthesis of plasma Proteins, synthesis of cholesterol, drug biotransformation. The primary function of the liver is to regulate all metabolic reactions in the body. The liver also serve as the manufacturing center of some non-functional plasma enzymes such as the transaminases, alkaline phosphatase, and acid phosphatase amongst others. Hepatotoxicity is defined in HIV patients when transaminases (Aspartate transaminase (AST)/glutamate oxaloacetate and/or Alanine transaminase (ALT)/glutamate pyruvate transaminase (GPT)) levels are above normal limit. Severe injuries to the liver are classified as grade 3 or 4 changes in AST and/or ALT during antiretroviral treatment when ALT, AST levels are 3-5 and greater than 5 times the upper normal limit [31]. These enzymes are non-functional plasma enzymes hence they have lower concentrations in plasma than in tissues, they have no physiological function in blood and their substrates are usually absent from plasma. Their presence in plasma is a clear

indication of an ongoing pathology in the liver or bone. Alkaline phosphatase is mainly produced from the hepatocytes and bone hence its elevation above normal limit is an indication of biliary obstruction, cholestasis or injury to the bile when bone disease is ruled out. Diseases of the bone such as Paget's disease, sarcoma, hyperparathyroidism, rickets and metastatic disease account for elevated alkaline phosphatase levels in plasma [31].

Generally, the therapeutic combination of antiretroviral drugs are non-nucleotide reverse transcriptase inhibitors (NNRTI's) plus nucleoside reverse transcriptase inhibitor (NRTI's) and a protease inhibitors (PI's) [32]. There is a great variation in the degree to which each of these drugs induce hepatotoxicity. Some studies conducted on the PI's full-dose rotanavir revealed that it has a severe hepatotoxicity [33, 34]. Some studies have also confirmed liver toxicity associated with Indinavir, Zidovudine Saquinavir [33]. It has been revealed that the grade of hepatotoxicity experienced some increase as the duration of treatment increases (table 1.0) [31]

Table 1.0: Comparison of hepatotoxicity among HAART experienced using AST and/or ALT with respect to duration on drug (In months)

	1-6 months		7-12 months		13-18months		>19 months	
Hepatotoxicity grade	**№**	**%**	**№**	**%**	**№**	**%**	**№**	**%**
Normal	4	33.3	11	57.9	30	60	9	47.4
0	5	41.7	1	5.3	7	14	3	15.8
1	3	25	5	26.3	9	18	4	21.1
2	0	0	2	10.5	2	4	1	5.3
3	0	0	0	0	2	4	2	10.5

Values expressed as absolute number (incidence), duration on drug is expressed in months

Source (Ngala et al, 2015)

Hepatotoxicity has also been common in HIV patients with Hepatitis B co-infection. Table 2.0 depicts the study where hepatotoxicity was observed in HIV patients with hepatitis B co-infection [31].

Table 2.0: Comparison of incidence of hepatotoxicity among cases and controls with Hepatitis B surface antigen (HBSAg) co-infection

	Cases(100)		Control(50)		Total	
Hepatotoxicity grade*	**№**	**percentage**	**№**	**percentage**	**№**	**percentage**
Normal	2	22.2	3	27.3	5	25
0	1	11.1	1	9.1	2	10
1	1	11.1	6	54.5	7	35
2	3	33.3	1	9.1	4	20
3	2	22.2	0	0	2	10

Values expressed as absolute number (incidence), *Hepatotoxicity grade of ALT and/or AST is used. Source (Ngala et al, 2015)*

With the above cited studies indicating the hepatotoxicity associated with HIV infection and its therapeutic intervention, one will ponder over the overall impact of HAART.

The Kidney and its associated HIV and HAART Pathologies

The kidney which is located retroperitoneal is endowed with a lot of functions. These include elimination of metabolic end products (urea, uric acid, creatinine etc.), elimination of foreign materials (drugs), maintain body fluid volume and composition (homeostatic regulation) thus regulate water-electrolyte balance, acid-base balance, blood pressure), regulate the production of renin, Production of erythropoietin, metabolize vitamin D to the active form (calcitriol) among others. Renal function tests measure glomerular function and tubular function. Glomerular filtration rate is measured based on the concept of clearance. Creatinine, urea and inulin are the substances measured to arrive at the function or dysfunction of the kidney.

The kidney plays a major role in the metabolism and excretion of antiretroviral drugs and this makes it liable to various types of injuries from some of these agents, including acute kidney

injury (AKI), tubulopathies, chronic kidney disease (CKD), and end-stage renal disease requiring renal replacement therapy. As the population of HIV-infected patients' ages and remains on HAART for longer periods of time, age-, HIV- and HAART-related metabolic disorders are increasingly being a challenge to the use of HAART. Both HIV-related and non-HIV-related pathologies can lead to renal pathologies observed in HIV patients. Drug reactions, hypertension, atherosclerosis, diabetes, primary and secondary nephropathies, as well as other infections are some of the non-HIV related conditions which can lead nephropathy in HIV patients [34]. HIV can cause direct injury to the kidneys as manifested by HIV-associated nephropathy (HIVAN). This entity was described before the era of HAART but continues to be a significant problem despite the advent of HAART [34-36]. HIVAN is the third leading cause of ESRD in African Americans who are also 18 times more likely to progress to ESRD than their white American counterparts [37]. A couple of years ago, HIVAN was considered to be genetically linked to a variation in the MYH9 locus of chromosome 22, which is found in 60% of African Americans and in less than 4% of Europeans [38]. However, recent researchers have noted that the MYH9 gene is located next to the APOL-1 gene which is more significantly associated with ESRD than all previously reported variations in MYH9 gene [39]. In low and low-middle income countries, patients do seek medical intervention at a late stage of HIVAN due to financial constraints and stigma. However, HIVAN does occur in HIV patients on HAART as a result of poor adherence to treatment modality. HIV thrombotic microangiopathy, HIVICK (HIV immune-complex kidney disease), as well as kidney disease associated with opportunistic infections such as cytomegalovirus, mycobacterium, cryptosporidium and malignancies such as lymphoma and Kaposi's sarcoma are some other form of HIV-related nephropathies [40-43]. Lesions in the glomerulus can also be associated with Hepatitis B (HBSAg) and Hepatitis C co-infections in seropositive HIV populace.

Acute Kidney Injury (AKI) that develops during HIV infection cannot be attributed to the sole and independent toxicity of the HAART rather, the severe opportunistic infections associated with HIV infection. HAART nephrotoxic effects accounted for 14% of late-onset AKI cases, occurring after 3 months of initiating HAART [44]. AKI in hospitalized HAART naïve HIV-1-infected patients is associated with a 6-fold higher risk of in-hospital mortality [45]. In the post-HAART era, HIV-infected patients with AKI still have an increased risk of in-hospital mortality, and these cases of AKI seem to be in the first annum of treatment [46] and this could be due to the late presentation of patients coupled with severe immunosuppression and concurrent infections at the time of admission.

Chronic Kidney Disease (CKD) also develops following HAART usage. Indinavir, atazanavir, and tenofovir are the major antiretroviral drugs involved in the genesis of CKD [47]. The Development of Antiretroviral Therapy in Africa (DART) trial examined 3,316 symptomatic ART-naive adults from Uganda and Zimbabwe with CD4 < 200cells/mm3 who were initiated on HAART with zidovudine-lamivudine plus tenofovir (74%), nevirapine (16%), or abacavir (9%). The study concluded that severe kidney dysfunction (<30mL/min as estimated by the Cockcroft-Gault formula) occurred in only 2.7% of patients on all regimens and kidney disease contributed to death in a minority of patients, which was generally related to concurrent disease [48]. The major limitation was that renal tubular function was not assessed. Although a low incidence (0.3 to 2%) is noted [49], tenofovir (TDF) is the drug most often associated with Fanconi syndrome (FS) [50], which carries the potential consequences of calcium and phosphorus dysregulation and osteomalacia [51, 52]. Following a meta-analysis of 17 studies (including 9 randomized, controlled trials) examining TDF safety, a significantly greater loss of kidney function among the TDF recipients, compared with control subjects (mean difference in calculated creatinine clearance, 3.92mL/min; 95%

confidence interval [CI], 2.13–5.70mL/min), as well as a greater AKI risk (risk di erence, 0.7%; 95% CI, 0.2–1.2), was noted [53].

There are several risk factors associated with nephrotoxicity and these factors are dependent on the characteristics of the patient and more importantly, the treatment modality under consideration notwithstanding hypertension, diabetes and other xenobiotics with nephrotoxic effects which are well known factors of grave concern in HIV patients on HAART [34, 54]. The widespread use of TDF in HIV patients with multiple co-infections has led to its assessment which revealed its nephrotoxic activities [48]. TDF-induced renal toxicity is more likely to occur in HIV patients with pre-existing kidney disease or poorly controlled HIV disease with longer overall antiviral treatment duration, older age, elevated baseline creatinine concentration, female gender, African American ethnicity, CD4 <200cells/mm^3, and concomitant administration of other nephrotoxic drugs [55, 56]. Combined therapy with TDF and protease inhibitors such as ritonavir appears to increase renal toxicity [57]. Conversely, HAART may increase the risk of hypertension, diabetes mellitus, and other metabolic complications creating a vicious cycle. In a study by Wyatt et al., the major risk factors for AKI and associated mortality included severe immunosuppression (CD4 count, <200cells/mm3) and opportunistic infections [19]. Dehydration, alkaline urine, and a previous history of nephrolithiasis appear to be risk factors for atazanavir associated kidney stones [58]. The risk factors for hyperlactemia (lactate > 2mmol/L with or without acidosis) which is common with “d-drugs” like stavudine (d4T) and didanosine (ddI) include extended duration of treatment, old age, female gender, pregnancy, hypertriglyceridemia, obesity, hepatitis C infection, impaired kidney function, treatment with ribavirin, and alcohol use [59, 60].

6.0 Dyslipidaemia

HAART regimens, especially those including protease inhibitors (PI) have shown to cause in a high proportion of HIV-infected patients, somatic (lipodystrophy /lipoatrophy) and metabolic (dyslipidemia, insulin resistance). These changes are associated with an increased risk of cardiovascular disease [61]. PI targets the catalytic region of HIV-1 protease [61]. This region is homologous with regions of two human proteins that regulate lipid metabolism thus, cytoplasmic retinoic-acid binding protein-1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP). Although without strong experimental support this homology may allow PIs to interfere with these proteins, which may be the cause of metabolic and somatic alterations that develop in PI-treated patients. The hypothesis is that PI inhibit CRABP-1-modified and cytochrome P450-3A-mediated synthesis of cis-9-retinoic acid and peroxisome proliferator-activated receptor type-gamma heterodimer. The inhibition increases the rate of apoptosis of adipocytes and reduces the rate at which pre-adipocytes differentiate into adipocytes, with the final effect of reducing triglyceride storage and increasing lipid release. PI-binding to LRP would impair hepatic chylomicron uptake and endothelial triglyceride clearance, resulting in hyperlipidemia and insulin resistance [61]. Moreover, there is also evidence that PI directly inhibit the uptake of glucose in insulin sensitive tissues, such as fat and skeletal muscle, by selectively inhibiting the glucose transporter Glut4 [61]. PIs are mainly responsible for insulin resistance [62]. Diabetes mellitus is a disease of abnormal glucose metabolism resulting in hyperglycemia due to either a deficiency of insulin secretion or insulin resistance.

Both insulin resistance and dyslipidemia are strongly related to body fat abnormalities observed in HIV patients on HAART. Impaired fat distribution consists of peripheral subcutaneous lipoatrophy and relative central fat accumulation. The use of antiretroviral drugs, especially for patients receiving regimens containing all three drug classes, and the duration of treatment are related to the presence and the severity of lypodistrophy [63].

NRTIs, especially stavudine, induce mitochondrial toxicity in subcutaneous fat tissues. Lypodystrophy occurs in coincidence with the other metabolic abnormalities, such as elevated total cholesterol, increase triglycerides and insulin resistance, and is associated with increased risk of hypertension and diabetes [61, 63]. It is well known that visceral fat accumulation represents a risk factor for cardiovascular disease hence annual body fat assessment is recommended. The drugs most associated with lipoatrophy are stavudine and zidovudine [63]. It has been revealed that HAART is independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4 to 6 years of HAART and that cumulative exposure to protease inhibitors (PIs) contributed to an increased rate of myocardial infarction in HIV patients which could partially but not fully be explained by dyslipidemia associated with the use of these drugs [61-63]. Patients on PI-based HAART are highly exposed to myocardial infarction [63]

7.0 Conclusion

The use of the only treatment modality for HIV and other therapies for HIV-related infections have been associated with short, medium and long-term toxicities on the liver, kidney and abnormal lipid metabolism. HAART can contribute directly to the elevation of non-functional plasma enzymes such as ALT, AST and ALP in the liver and when these are coupled with hepatitis B and /or hepatitis C co-infections, it creates an urgent need for the discontinuation of treatment. Likewise HAART can engineer renal dysfunction by inducing acute tubular necrosis, acute interstitial nephritis, crystal nephropathy and renal tubular disorders or renal dysfunction indirectly through drug interaction or biotransformation. Abnormal fat and lipid metabolism, which are risk factors for cardiovascular diseases can also be attributed to the use of HAART. It is therefore pertinent to screen HIV patients for any liver, kidney and heart associated diseases prior to treatment initiation and also monitor renal, liver and cardiac function even as they remain on HAART.

References

1. WHO: Prevalence of Human Immunodeficiency Virus. World Health organization publication, 2016
2. Ferguson MR, Rojo DR, von Lindern JJ and O'Brien WA. HIV-1 replication cycle. Clinical Laboratory Medicine 2002; 22: 611-35.
3. Greene WC. AIDS and the immune system. Sci Am 1993; 269, 98-105.
4. Wiredu OK, Edzeamey FJ, Dompreh A, Gborgblorvor D, Maxwell Awuah M, Ako AK et al. Correlation of Haematological Parameters with TNF-α and Interleukin (IL-6) in Seropositive HIV Patients on Highly Active Antiretroviral Therapy (HAART) and HAART Naïve patients. International journal of Research and Reports in Haematology 2018, 1(1):1-7
5. Cunningham AL, Donaghy H, Harman AN, Kim M and Turville SG. Manipulation of dendritic cell function by viruses. Curr Opin Microbiol 2010; 13, 524-9.
6. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med 2004; 200:749-59.
7. Veazey RS, Marx PA and Lackner AA. Vaginal CD4+ T cells express high levels of CCR5 and are rapidly depleted in simian immunodeficiency virus infection. Journal of Infectious Diseases 2003; 187, 769-76.
8. Roederer M, Dubs JG, Anderson MT, Raju PA, Herzenberg LA and Herzenberg LA. CD8 naive T cell counts decrease progressively in HIVinfected adults. Journal of Clinical Investigation 1995, 95: 2061-6.
9. Mahalingam M, Peakman M, Davies ET, Pozniak A, McManus TJ and Vergani D. T cell activation and disease severity in HIV infection. Clinical Experimental Immunology 1993, 93:337-43.

10. Bass H Z, Nishanian P, Hardy WD, Mitsuyasu RT, Esmail E, Cumberland W and Fahey JL. Immune changes in HIV-1 infection: significant correlations and differences in serum markers and lymphoid phenotypic antigens. Clin Immunol Immunopathol 1992, 64:63-70.
11. Aukrust P, Liabakk NB, Muller F, Espevik T and Froland SS. Activation of tumor necrosis factor--alpha system in HIV-1 infection: association with markers of immune activation. Infection 1995a, 23:9-15.
12. Wiredu OK, Edzeamey FJ, Dompreh A, Awuah M, Ako AK, Sampong BB et al. Lymphocyte Subset (CD3, CD4 and CD8 Cells) and their Ratios in HIV patients on Highly Active Antiretroviral Therapy (HAART) and HAART Naïve Patients. International Journal of Microbiology and Advanced Immunology 2018; 06(2):92-95.
13. Douek DC, Brenchley JM, Betts MR, Ambrozak DR, Hill BJ, Okamoto Y et al. HIV preferentially infects HIV-specific CD4+ T cells. Nature 2002, 417, 95-8.
14. Margolick JB, Munoz A, Donnenberg AD, Park LP, Galai N, Giorgi JV et al. Failure of T-cell homeostasis preceding AIDS in HIV-1 infection. The Multicenter AIDS Cohort Study. Nat Med 1995, 1:674-80.
15. Connick EM, Lederman MM, Kotzin BL, Spritzler J, Kuritzkes DR, St Clair M et al. Immune reconstitution in the first year of potent antiretroviral therapy and its relationship to virologic response. Journal of Infectious Diseases 2000, 181, 358-63.
16. Kalayjian RC, Landay CA, Pollard RB, Taub DD, Gross BH, Francis IR et al. Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. Journal of Infectious Diseases 2003, 187:1924-33.

17. Lederman MM, McKinnis R, Kelleher D, Cutrell A, Mellors J, Neisler M, Cooney E, Haas DW et al. Cellular restoration in HIV infected persons treated with abacavir and a protease inhibitor: age inversely predicts naive CD4 cell count increase. AIDS 2000, 14, 2635-42.
18. Gandhi RT, Spritzler J, Chan E, Asmuth DM, Rodriguez B, Merigan TC et al. Effect of baseline- and treatment-related factors on immunologic recovery after initiation of antiretroviral therapy in HIV-1-positive subjects: results from ACTG 384. Journal Acquired Immune Deficiency Syndromes 2006, 42, 426-34.
19. Wood E, Yip B, Hogg RS, Sherlock CH, Jahnke N, Harrigan RP et al. Full suppression of viral load is needed to achieve an optimal CD4 cell count response among patients on triple drug antiretroviral therapy. Aids 2000, 14:1955-60.
20. Teixeira L, Valdez H, McCune JM, Koup RA, Badley AD, Hellerstein MK et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. Aids 2001, 15:1749-56.
21. Viard JP, Mocroft A, Chiesi A, Kirk O, Roge B, Panos G et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the Euro SIDA study. J Infect Dis 2001, 183:1290-4.
22. Hunt PW, Cao HL, Muzoora C, Ssewanyana I, Bennett J, Emenyonu N et al. Impact of CD8+ T-cell activation on CD4+ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy. AIDS 2011, 25:2123-31
23. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus co-infection: the Swiss HIV Cohort Study. Lancet 2000, 356:1800-5.

24. Goicoechea M, Smith DM, Liu L, May S, Tenorio AR, Ignacio CC et al. Determinants of CD4+ T cell recovery during suppressive antiretroviral therapy: association of immune activation, T cell maturation markers, and cellular HIV-1 DNA. Journal of Infectious Disease 2006, 194: 29-37.

25. Valdez H, Connick E, Smith KY, Lederman MM, Bosch RJ, Kim RS et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. Aids 2002, 16:1859-66.

26. French MA, King MS, Tschampa JM, da Silva BA and Landay AL. Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4+ T cells. Journal of Infectious Disease 2009, 200:1212-5.

27. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008, 5:203.

28. Dalgleish A, Beverly P, Clampham P. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 1984; 312: 763:767

29. Poveda E, Briz V and Soriano V. Enfuvirtide, the first fusion inhibitor to treat HIV infection. AIDS Rev 2005; 7: 139-147

30. Weiss C. HIV-1 gp41: Mediator of fusion and target for inhibition. AIDS Rev 2003; 5:214-221

31. Ngala RA, Opoku D and Asare G. Effects of HIV infection and Highly Active Antiretroviral Therapy (HAART) on the liver of HIV patients. Trends in medical research 2015, 10(1):1-11

32. Young B. Review: Mixing new cocktails. Drug interactions in antiretroviral regimens AIDS Patient Care and STDs 2005 19: 286-297

33. Bonfanti PS, Landonio E, Ricci C, Martenelli P, Fortuna R, Faggion I and Quirino T. Risk factors for hepatotoxicity in patients treated with HAART. Journal of Acquired immunodeficiency syndromes 2001, 27: 316-318

34. Campbell LJ, Ibrahim F, Fisher M, Holt SG, Hendry BM and Post FA. Spectrum of chronic kidney disease in HIV-infected patients. HIV Medicine 2009, 10(6):329–336

35. Hegde S, Singh C and Ohare B. HIV-associated nephropathy in the setting of maximal virologic suppression. Pediatric Nephrology 2011, 26(6):973–977.

36. Choi AI, Shlipak MG, Hunt PW, Martin JN, and Deeks SG. HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy. AIDS 2009, 23 (16):2143–2149.

37. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J and Moore RD. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. Journal of Infectious Diseases 2008; 197(11):1548–1557.

38. Kopp JB, Smith MW and Nelson GW. MYH9 is a major-e ect risk gene for focal segmental glomerulosclerosis. Nature Genetics 2008, 40(10):1175–1184.

39. Tzur S, Rosset S and Shemer R. Missense mutations in the APOL1 gene are highly associated with end stage kidney diseaseriskpreviouslyattributedtotheMYH9gene. Human Genetics 2010, 128(3):345–350.

40. Gerntholtz TE, Goetsch SJW and Katz I (2006). HIV related nephropathy: a South African perspective. Kidney International 2006, 69(10):1885–1891.

41. Tamkus D, Jajeh A, Osafo D, Hadad L, Bhanot B and YogoreIII MG. Thrombotic microangiopathy syndrome asan AIDS-defining illness: the experience of J. Stroger hospital of Cookcounty. Clinical Advances in Hematology and Oncology 2006, 4(2):145–149.

42. Brady MT, Oleske JM, and Williams. Declines in mortality rates and changes in causes of death in HIV-1 infected children during the HAART era. Journal of Acquired Immune Deficiency Syndromes 2010, 53(1):86–94.

43. Pollok RCG, Francis N, Cli S, Nelson N, and Gazzard B. Kaposi's sarcoma in the kidney. International Journal of STD and AIDS 1995, 6(4):289–290.

44. Roe J, Campbell LJ, Ibrahim F, Hendry BM, and Post FA. HIV care and the incidence of acute renal failure. Clinical Infectious Diseases 2008, 47(2):242–249.

45. Wyatt CM, Arons RR, Klotman PE and Klotman ME. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. AIDS 2006, 20(4):561–565.

46. Naicker S, Aboud O, and Gharbi MB. Epidemiology of acute kidney injury in Africa. Seminars in Nephrology 2008, 28(4):348–353.

47. Atta MG, Deray G and Lucas GM (2008). Antiretroviral nephrotoxicities. Seminars in Nephrology, 28(6):563–575.

48. Reid A, St¨ohr W and Walker AS. Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy. Clinical Infectious Diseases 2008, 46(8):1271– 1281.

49. Jones R, Stebbing J and Nelson M. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: a cohort and case-control study. Journal of Acquired Immune Deficiency Syndromes 2004, 37(4):1489–1495.

50. Izzedine H, Isnard-Bagnis C and Hulot. Renal safety of tenofovir in HIV treatment-experienced patients. AIDS 2004, 18(7):1074–1076.

51. Earle KE, Seneviratne T, Shaker J and Shoback D. Fanconi's syndrome in HIV+ adults: report of three cases and literature review. Journal of Bone and Mineral Research 2004, 19(5):714–721.

52. Peyri'ere H, Reynes J, and Rouanet I. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases,"Journal of Acquired Immune Deficiency Syndromes 2004. 35(3), 269–273.

53. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, and M.Tonelli. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in hiv-infected patients," Clinical Infectious Diseases 2010, 51(5):496–505.

54. Overton ET, Nurutdinova D, Freeman J, Seyfried W, and Mondy KE. Factors associated with renal dysfunction within an urban HIV-infected cohort in the era of highly active antiretroviral therapy," HIV Medicine 2009, 10(6):343–350.

55. Crum-Cianflone N, Ganesan A, and Teneza-Mora N. Prevalence and factors associated with renal dysfunction among HIV infected patients. AIDS Patient Care and STDs 2010, 24(6):353–360.

56. Nelson M, Azwa A, Sokwala A, Harania RS, and Stebbing J. Fanconi syndrome and lactic acidosis associated with stavudine and lamivudine therapy. AIDS 2008, 22(11):1374–1376.

57. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Ho man R, and Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. Clinical Infectious Diseases 2006, 42(2):283–290.

58. Couzigou C, Daudon M and Meynard JL. Urolithiasis in HIV-positive patients treated with atazanavir. Clinical Infectious Diseases 2007, 45(8):105–108.

59. Murphy MD, O'Hearn M and Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine," Clinical Infectious Diseases 2003, 36(8):1082–1085.

60. Bonnet F, Balestre E, Bernardin E, Pellegrin JL, Neau D, and Dabis F. Risk factors for hyperlactataemia in HIV infected patients, Aquitaine Cohort, 1999–2003. Antiviral Chemistry and Chemotherapy 2005, 16(1):63–67.

61. Barbaro G, and da Silva EF. Cardiovascular Complications in the acquired immunodeficiency syndrome. Rev Assoc Med Bras 2009; 55(5): 621–30

62. Hima Bindu A, Naga Anusha P. Adverse Effects of Highly Active Anti-Retroviral Therapy (HAART). J Antivir Antiretrovir 2011, 3: 060-064

63. Thienemann F, Sliwa K and Rockstroh JK. HIV and the heart: the impact of antiretroviraltherapy: a global perspective. European Heart Journal (2013)34, 3538–3546.