LAMK Lahden ammattikorkeakoulu
Lahti University of Applied Sciences

FACTORS LEADING TO FASTER PROGRESSION OF HIV TO AIDS

LITERATURE REVIEW

LAHTI UNIVERSITY OF APPLIED SCIENCES LTD
Degree programme in Nursing
Thesis
Autumn 2018
Kipchirchir Lagat

Lahti University of Applied Sciences
Degree Programme in Nursing

Lagat, Kipchirchir:

Title: Factors leading to faster progression of HIV to AIDS
Subtitle: Literature Review

Bachelor's Thesis in HIV/AIDS 54 pages

Autumn 2018

ABSTRACT

The extreme differences experienced in the rate of HIV to AIDS progression have received remarkable interest from medical researchers. Nevertheless, despite the increased attention the phenomenon has received, recent reports highlight that the factors influencing the progression are not fully understood. Researchers have however attributed the progression of HIV to AID to various factors that include viral genetic factors, host immune responses and environmental co-factors. Some of the viral factors that have been evidenced to influence progression include viral subtype, co-receptor use and presence of deleterious mutations in the virus. Host factors include elements such as age, ethnicity, gender, psychosocial, CYP polymorphism, HLA and body mass index. Environmental factors include socio-economic status and mode of transmission. The purpose of this review was to highlight the progress and changes that have taken place over the past few years in relation to the use of newly identified biomarkers that predict HIV disease progression. A literature review was undertaken to synthesis findings from a wide array of scholarly researches published between 2010-2018 to develop definitive findings and gain new understanding on the subject matter. The study particularly focuses on the progress that has been achieved in explaining some of the factors that might contribute to faster HIV disease progression in resource restrained regions. Current evidence suggests that differences in demographic, education, social, cultural and economic factors between developed and developing countries may contribute to variability in the rate of HIV disease progression. Therefore, in order for nurse's practitioners to design effective intervention and prevention programs, it is vital to consider social and cultural variations.

Key words: HIV, AIDS, Progression, Immunological factors, Host factors, Virological factors

Lahden ammattikorkeakoulu

Sosiaali ja Terveyshuolto; Sairaanhoitaja.

Lagat, Kipchirchir:

HIV:n nopeampaan etenemiseen AIDSiin johtuvat tekijät. Kirjallisuuskatsaus

Suuntautumisvaihtoehdon opinnäytetyö, 54 sivua

Syksy 2018

TIIVISTELMÄ

Merkittävä vaihtelu HIV ja AIDS tartuntojen määrän kasvussa on saanut suurta huomiota lääketieteellisiltä tutkijoilta. Huolimatta alati kasvavasta huomiosta tätä ilmiötä kohtaan, viime aikaiset raportit osoittavat, että tartuntojen määrän kasvun vaihtelun syitä ei täysin ymmärretä. Tutkijat ovat kuitenkin määritelleet HIV:in ja AIDS:in levinneisyyden johtuvan monista eri tekijöistä, muun muassa viruksen aiheuttamat geneettiset tekijät, elimistön vastustuskyky ja ympäristön myötävaikuttajat. Joidenkin virusperäisten tekijöiden on todistettu vaikuttavan levinneisyyteen, esimerkiksi viruksen alatyyppi, apureseptorin hyödyntäminen tai vahingollisten virusmuunnosten läsnäolo. Elimistöstä johtuvia tekijöitä ovat ikä, etnisyys, sukupuoli, psykososiaalisuus, CYP polymorfismi, HLA ja kehon painoindeksi. Ympäristöllisiä tekijöitä ovat sosioekonominen asema ja vuorovaikutustila. Tämän arvion tarkoitus oli korostaa edistymistä ja muutoksia, mitä on tapahtunut viimeisen muutaman vuoden aikana suhteessa vastikään havaittuihin biologisiin merkkiaineisiin, joiden käyttö ennustaa HIV-tartuntojen kasvua. Kirjallisuuden arvioiminen yhdessä tutkijoiden julkaisemien tutkimusten kanssa vuosilta 2010-2018 selvensi löydöksiä ja auttoi ymmärtämään aihetta uudella tavalla. Tutkimus keskittyy erityisesti siihen edistykseen, mikä on saavutettu syiden selittämiseksi, mitkä voivat vaikuttaa HIV-tartunnan nopeampaan etenemiseen alueilla, missä resurssit ovat rajoitetut. Tämän hetken todisteet vihjaavat siihen, että väestörakenteen erot; koulutus, sosiaaliset, kulttuuriset ja taloudelliset tekijät kehitysmaiden ja hyvinvointimaiden välillä voi vaikuttaa HIV-tartuntojen määrän kasvun vaihteluun. Sen vuoksi on erittäin tärkeää käsittää sosiaaliset ja kulttuurilliset vaihtelut, jotta terveydenhoitoa harjoittavat voivat suunnitella, kuinka puuttua ongelmaan ja kuinka estää tartuntoja mahdollisimman tehokkaasti. Avainsanat: HIV, AIDS, tartunnat, levinneisyys, vastustuskyvystä johtuvat tekijät, elimistötekijät, virustekjiät.

CONTENTS

Table of Contents

1 INTRODUCTION

1.1 Background Information

The human immunodeficiency virus (HIV) was first discovered in the early 1980s among homosexual men in the United States. Infection with HIV virus contributes to the progressive destruction of the human immune system and eventually culminating into acquired immunodeficiency syndrome (AIDS). From the beginning of the epidemic, AIDS- related illnesses have led to more than 35.4 million deaths globally (UNAIDS, 2018, 14). Though HIV-1 has been the most studied infectious agent for the past three decades, the development effective treatment options have made slow progress. Nevertheless, advances in the use of highly active antiretroviral therapy (HAART) have revolutionized the management of the disease by delaying the progression of HIV to AIDS.

Clinical trials have particularly evidenced profound reductions in mortality among patients infected with HIV from the combination antiretroviral therapy. Notwithstanding current improvements in HIV prevention through education and access to HIV antiretroviral drugs, the pandemic has continued to outpace global efforts.

The appearance of clinical markers of HIV infection has been determined to be consistent in most infected people whereas the rate of disease progression has shown remarkable variation. Among HIV positive persons that are not under HAART therapy, the latent period between infection and manifestation of AIDS has been reported to average about 7.7 to 11 years (Moreno 2014, 213). Nevertheless, there are other distinctive groups of infected individuals that develop AIDS more rapidly in less than 5 years, and others maintain a stable immune function for more than 10 years without ART therapy. The biological basis contributing to the extreme differences experienced in the rate of HIV to AIDS progression has not been fully understood.

The variability in progression of HIV to AIDS has been attributed to multiple factors such as viral genetic factors, host immune responses and environmental co-factors (Müller, Fraser & Herbeck 2011; Langford, Ananworanich & Cooper, 2007; Moreno, 2014). Some of the viral factors that have been evidenced to influence progression include viral subtype, co-receptor use and presence of deleterious mutations in the virus. Host factors include elements

such as age, ethnicity, gender, psychosocial, CYP polymorphism, HLA and body mass index. Environmental factors include socio-economic status and mode of transmission. A combination of these factors dictates the rate that the HIV progresses into AIDS by dictating how fast the virus is able to replicate and overcome the host's immunity.

Globally, HIV/AIDS remains as one of the major causes of death. Based on the latest available data from UNAIDS (2018), over 36.9 million people were HIV positive in 2017. According to UNAIDS report; from the beginning of the epidemic, AIDS- related illnesses have led to more than 35.4 million deaths globally. Clinicians who deal with HIV positive patients rely on various immune system indicators that highlight increased progression of the disease. These prognostic tests are vital especially during the clinical latency phase, monitoring an individual's response to antiviral treatment and hence utilized to supplement other clinical parameters (Gupta & Gupta 2004, 7).

The HIV-1 virus can be further classified into four distinctive groups that include M, O, N and P (Major, Outlier, New and Pending respectively), where M group accounts for the group with the highest infection rate. Though the appearance of clinical markers of HIV infection have been determined to be consistent in most infected people, the rate of disease progression has shown remarkable variation. Researchers have attributed the progression of HIV to AIDS to various factors that include environmental, host and virology factors.

Another major factor that has contributed to varying outcomes in most studies is associated with the different HIV-1 subtypes. Fauci 2007, (206) claims that a large proportion of about 80% of HIV infection follow a standard pattern of progression, where AIDS develop 7.7 to 11 years after infection. Following HIV virus transmission, the early or acute phase of infection is linked to a high loss of viremia CD4+ T-cells in the blood system and mucosal lymphoid tissues.

1.2 Statement of the Problem

According to the United Nations Development Program (UNDP 2005), HIV has caused the “single greatest reversal in human development” in modern history. Despite HIV-1 being the most studied infectious agent for the past three decades, the development effective treatment options have made slow progress. Nevertheless, researchers have been able to effectively utilize new and advanced technologies which have expanded our knowledge related to the structure and replication of the virus. Based on latest available data from UNAIDS (2018), over 36.9 million people were HIV positive in 2017. Alongside UNAIDS report that from the beginning of the epidemic, AIDS- related illnesses have led to more than 35.4 million deaths globally.

1.3 Justification

The majority of studies attempting to study the contribution of various factors on the disease progression are concentrated in developed countries. However, it is recognized that resource limited regions harbor the greatest burden related to HIV/AIDS disease. The study of some of the factors that may be involved in the faster progression of the virus among infected individuals becomes necessary to improve management and the administration of HAART.

1.4 Objectives

- To find out the relationship between viral replication and hosts’ immune responses
- To identify the relationship between inflammation and immune activation on the rapid progression of HIV
- To point out the main hosts and viral factors involved in severe progression of HIV-1.

- To ascertain the role of environmental co-factors in the progression of HIV-1 disease

1.4.1 Purpose of the thesis

The purpose of this review is to highlight the progress and changes that have taken place over the past few years in relation to the use of newly identified biomarkers that predict HIV disease progression.

The study will particularly focus on the progress that has been achieved in explaining some of the factors that might contribute to faster HIV disease progression in resource restrained regions. This will be of importance to nurses in understanding the nature of the disease and therefore plan and implement appropriate care for patients.

1.5 What factors influence the progression of HIV to AIDS?

The study will be expected to extend current research on some of the factors that impact on the progression of the disease, which can be used as a valuable guide to improve the effective management and control of the disease. An improved understanding of the factors that promote HIV progression will be vital for the design of enhanced preventive and therapeutic approaches. Traditionally, clinicians have attempted to characterize the progression of HIV to AIDS to changes in baseline CD4+ T cell counts and HIV RNA load, which are some of known pathological changes that occur to the cellular immune system. However, CD4+ T cell count and HIV RNA load only explain only up to about 30% and 47% respectively of the variability from HIV infection to AIDS (McKay 2014). The information can also be used to promote the development of updated diagnostic methodologies aimed at improving the accuracy of early virus antibodies and antigens that are vital for limiting progression of the disease and applying more timely treatment regimens. The use of biomarkers in the diagnosis of

cardiovascular diseases and other genetic and immune disorders is well known. Nevertheless, finding a reliable biomarker that can be used to predict early HIV infection still remains a significant challenge to date. Therefore, this study is expected to offer a comprehensive analysis of possible biomarkers that can be used to analyze the mechanisms that underlie pathogenic processes.

2 LITERATURE REVIEW

2.1 HIV Virus

HIV is a member of a class of viruses that are referred to as retroviruses. There are two types of HIV viruses that are known to cause AIDS, which include HIV-1 and HIV-2. Both types share many similarities that include transmission modes, intracellular replication mechanisms and clinical outcomes (Klatt 2018, 86). As the disease continue to progress, patients infected with HIV-2 virus also become susceptible to the same category of opportunistic diseases similar to ones infected with HIV-1. Despite the clear similarities between the two viruses, they however exhibit differences in virus evolution, targets of infection and pathogenic capacity. The major clinical differences between the types of infections caused by the two viruses relates to the rate of progression to immunodeficiency, which occurs faster in HIV-1 compared to HIV-2. According to Moreno 2014, 33, people with the HIV-2 virus infection have a comparatively longer asymptomatic phase, lower levels of viral RNA and report higher CD4 lymphocyte count. One of the unique factors that distinguish AIDS from other infections is the comparatively long latent period before the infected person develops any visible symptoms. Geographically, HIV-1 is the most prevalent across the globe while HIV-2 is confined in parts of West Africa and Portugal.

2.1.1 Modes of Transmission and Groups at risk of HIV infection

HIV-1 is transmitted via three major routes that include sexual contact, exposure to infected blood and vertical transmission. Langford, Ananworanich & Cooper (2007, 16), underline that over 80% of all HIV-1 infections are caused by sexual transmission that arises from mucosal surfaces exposure to the virus. Other factors that increase the risk to HIV infection during intimacy include high viral

load or concurrent sexually transmitted diseases among the partners. Vertical, or mother-fetus HIV transmission may occur during the pregnancy period, breast feeding or during delivery.

2.1.2 Diagnosis, Treatment and Control of HIV

The control of HIV disease has been achieved through the combination of various HAART treatment options. Reduction and stabilization of the disease has also been achieved through targeting of high-risk groups with education campaigns and increased access to condoms and ARV drugs. The use of antiretroviral therapies has been complicated by high HIV drug resistance that arises from the mutable nature of the virus that may negate the efficiency of the drugs (Venkataramana, 2013).

2.2 Pathogenesis

Like other retroviruses, HIV does not contain deoxyribonucleic acid (DNA) and cannot also replicate outside the host cells. The pathogenesis of HIV infection has been described to be a product of the life cycle of the virus, cellular environment of the host and number of viruses in the infected person (Fanales-Belasio et al., 2010, 5). After entering the body, HIV virions are attracted to cells containing appropriate CD4 receptor molecule where they can get inside susceptible cells leading to the initial infection. Thus Klimas, Koneru and Fletcher (2008, 45) underline that probability of infection is dependent on the amount of ineffective HIV vitrons within the body fluids of the host and the number of available cells that contain enough CD4 receptors. The dissemination of the infection through the bloodstream and into secondary lymphoid organs requires local viral expansion of the infection.

On reaching the lymphoid tissues, favorable conditions grant the virus access to a high number of susceptible cells which leads to an exponential increase of infected cells and viral RNA. Though the peripheral blood contains little detectable virus during the clinical latency period of HIV infection, viral replication remains active in lymphoid tissues. During early HIV infection, viral load can lead to millions of virions per one ml of blood. Following HIV infection of hosts, Moreno (2014, 13), highlights that the body tries to develop adaptive immune responses that are directed against viral antigens. Nevertheless, the host is unable to clear the infection, which further contributes to the gradual degeneration of CD4+ T cells.

2.2.1 Phases of HIV Infection

HIV infection is associated with the continuous depletion of $CD4^+$ T cells, immune activation and the subsequent decline of immunological function, which leads to the eventual onset of AIDS (Silva et al., 2010, 65). In majority of HIV infections, clinical manifestations of AIDS can take a period of 7 to 11 years. The course of HIV-1 infection can be distinguished into three major phases from the period of infection to advanced disease as shown in Figure 1 below.

2.2.1.1 Acute

The acute infection phase lasts for 2 to 6 weeks following infection, up until the point where anti-HIV-1 antibodies can be detected. The first 7-21 days that follow transmission is referred to as the ‘eclipse phase’, since HIV-1 is not detectable in the blood plasma (Hernandez-Vargas & Middleton, 2013, 65). After this point, plasma viremia replicates and increases exponentially while the levels of CD4+ T lymphocytes begin to decline significantly.

However, immune responses are able to partially stabilize and control the high levels of viremia during the first few weeks up to a specific set point. The number of blood's $CD4^+$ T cells and viral set point levels also act as clinically useful predictors of HIV progression (Ho et al., 2005, 43). During the initial infection period, most people experience symptoms such as fever and rash while about 30% remain asymptomatic. The symptoms that accompany acute HIV-1 infection may not therefore arouse clinical suspicion. The most common test in this phase is undertaken to detect the presence of p24 antigen which may not always be positive.

2.2.1.2 Chronic Phase

Acute infection is then accompanied by the chronic phase, which involves a gradual decline in HIV viremia levels and lack of symptoms. This phase is also referred to as the clinical asymptomatic period. According to Klatt (2016, 113), these observations reflect antiviral action that arises from continuous stimulation of innate and adaptive immune responses. Specifically, antibodies bind to HIV antigens in order to prevent the infection of cells in a process referred to as neutralization of infectivity. Nevertheless, the HIV virus can recognize virus antigens where it eliminates them through development of antigen-specific cytotoxic mechanisms. During this phase, the HIV virus is able to counteract antiviral immunity, continue replicating and subsequently inducing systemic inflammation. Langford, Ananworanich and Cooper (2007, 15), ascribe the inability of the antiviral immunity to eradicate HIV virus to several factors. The most effective mechanisms developed by the HIV virus include the persistence of integrated virus in lymphoid organ reservoirs and high rate of mutations in the virus genome.

The mutation of HIV virus leads to the emergence of new HIV subtypes, which according to Klatt (2016, 117) can explain HIV's antiretroviral drug resistance during infection. Virus replication continues in the lymphoid compartment where peaks of HIV viremia are detected in the plasma. The presence of viremia as detected through the use of laboratory tests underlines the inability of the immune system to effectively control the virus (Fanales-Belasio et al., 2010, 76). This asymptomatic phase is also associated with the slow but gradual loss of CD4+ T cells where they decrease more rapidly than they are produced. Subsequently, the shift in the equilibrium between the rate of T cells production and destruction further contributes in the impairment of the immune system. In absence of ARV treatment over half of HIV infected persons may develop signs of the disease following a median of 10 years of infection. Nevertheless, the rate of immune progression is dependent on various host and viral factors which are the focus of this study and will be evaluated in detail in the next section.

2.2.1.3 AIDS Stage

The asymptomatic phase is then followed with the AIDS stage, which involves the simultaneous depletion of $CD4^+$ T cell count and increased viral load, resulting in a deterioration of the immune response. AIDS is the final stage that is characterized by a very low $CD4^+$ T-cell count of less than 200 cells/µl (Venkataramana, 2013, 17). Such a situation leads to the onset of opportunistic infections such as HIV-1 associated kidney failure, cancers and degeneration of nervous system which further increases the risk of mortality. Clinical symptoms of AIDS phase include severe reduction of body weight, lymph node swelling and fever (Lama & Planelles, 2007, 133). Continuous degradation of $CD4^+$ T can further increase the risks of developing anemia. Nevertheless, the progression of

the disease into the AIDS phase varies considerably depending on factors such as antiviral response of the host and ability to contain replication.

The clinically latent period between HIV virus exposure and appearance of visible signs of infection varies significantly among infected persons. On average Müller, Fraser and Herbeck (2011) highlight that up to 80% of infections follow an average rate of progression where they take between 6 to 10 years to develop AIDS without antiretroviral treatment. Another group representing roughly 10% of infected individuals experience rapid progression to AIDS in less than 5 years. The last category of infected persons report a slow progression profile where they may take more than 10 years to develop AIDS without treatment. These sub-groups are categorized as typical progressors, rapid progressors, long-term nonprogressors, and elite controllers.

Up to now Fanales-Belasio et al. (2010, 65), underline that no study has evidenced the failure of HIV-infected individuals to develop to AIDS.

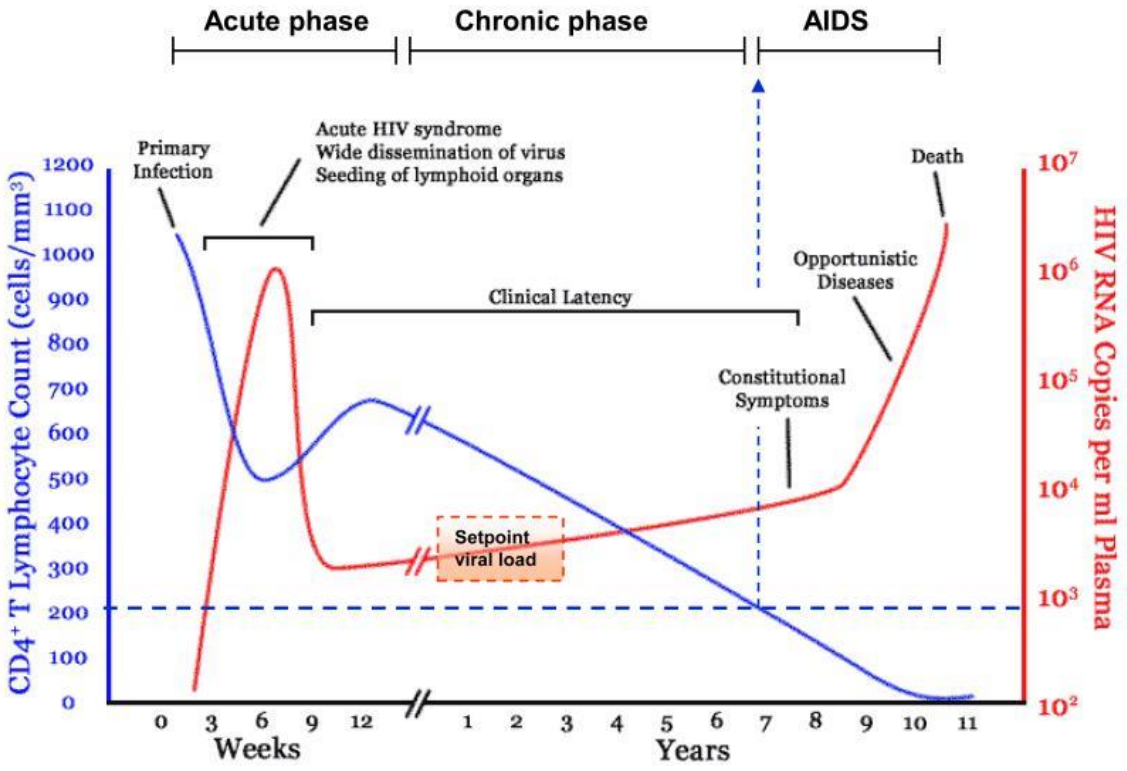

Figure 1: The typical phases of HIV infection illustrated by the varying CD4⁺ T-cell and viral RNA load counts recorded during the course of HIV infection. Adapted from: (An & Winkler, 2010).

2.2.2 Groups of Progression

Based on their rate of progression, HIV positive individuals can be categorized into 4 groups that include: typical progressors, rapid progressors, long-term nonprogressors, and elite controllers. The majority of this population comprises the typical progressors that have an average latent HIV infection period of between 7 to 10 years before appearance of clinical AIDS (Fauci, 2007, 65). Comprising the majority of all HIV cases, they are able to develop various HIV

variants that replicate slowly up until more rapidly replicating variants emerge in the course of progression to AIDS.

2.2.2.1 Elite Controllers

The ‘elite controllers’ category represents a unique group of HIV infected individuals that are able to control the infection and replication of HIV for many years without antiretroviral treatment (Venkataramana, 2013, 65). Research studies have used various unique characteristics to define elite controllers. One of their unique characteristics is that they develop asymptomatic HIV infection that is associated with significantly low rates of $CD4^+$ T-cell loss, which averages 18 cells/µl/year (O’Connell, Bailey & Blankson, 2009; Hernandez-Vargas & Middleton, 2013). In particular, they are able to maintain low T cell depletion for more than 10 year after seroconversion which is the period of time that HIV antibodies become detectable in the acute stage of HIV infection. Secondly, Moreno (2014) underlines that even in the absence of antiretroviral drugs, the group is able to suppress the levels of plasma HIV-1 RNA below the 50 copies/ml level required for detection for more than a year. The third and least common characteristic associated with the group is that they experience only limited episodes of viremia. Langford, Ananworanich and Cooper (2007, 8) associate this feature with the ability of their immune systems to regain control quickly following primary infection. This group has received special attention from researchers where they have been intensively studied as a model of understanding HIV control mechanisms. Elite controllers have been estimated to account for 0.3% of all HIV infected individuals (Klatt, 2016, 83).

2.2.2.2 Rapid progressors

Accounting for about 10% of HIV-infected persons, these groups progress to AIDS within a year after infection without treatment. During the acute HIV phase, some of them have also been reported to exhibit clinically severe presentations including some of the symptoms that define AIDS (Müller, Fraser & Herbeck, 2011, 205). Studies have established that during the acute phase, these people also have high viral loads that do not fall to levels that are seen among typical progressors due to infection with multiple strains of HIV virus. Unlike elite controllers, studies focusing on rapid progressors are scant, which has been attributed to difficulty to identify and recruit such patients. Existing research has often produced incontinent results which have hampered the ability to accurately explain the rapid progression among this group. Nevertheless, this group can be defined by various criteria which normally include high levels of viremia and progressive immunosuppression that accompanies seroconversion (Fanales-Belasio et al. 2010, 6). Studies have hypothesized that accelerated disease progression arises from a complex interplay between a number of host and viral factors.

2.2.2.3 Viremic non progressors

The high HIV-1 replication that occurs in the chronic stage of HIV infection is linked to high rate of disease progression. However, the viremic or long-term progressors are able to tolerate high levels of plasma viral loads while also remaining asymptomatic during this stage (Hernandez-Vargas & Middleton, 2013, 45). Long-term progressors also record persistently high levels of CD4+ T-cells that typically averages around 500copies/μL, which is lower than that of elite controllers which ranges between 200 and1000 copies/μL (Klatt, 2016, 254). Similar to rapid progressors, viremic non-progressors account for a small

proportion of HIV infected populations which makes it challenging for researchers to generate accurate representation of their immunopathogenesis.

2.3 Inflammation and immune activation in HIV

2.3.1 CD4+ T-cells homeostasis and depletion

Given that the HIV virus targets cells of the host's immune system, the entire course of HIV infection is characterized by elevated immune activation and chronic inflammation. According to Brenchley et al. (2016, 38), the immune system serves three major functions that include recognition and eradication of foreign antigens, developing tolerance to self-antigens and building immunologic memory. The human immune system comprises of two systems: a) Innate immune system passed along from evolution and 2) Adaptive immune system that responds against specific threats. HIV virus primarily targets the $CD4^+$ T cells which are involved in the mediation and activation of some of the immune response cells. At the infected site, $CD4^+$ T cells account for 80% of all infected cells and over 90% of infected cells in the lymphatic system (Klatt, 2018, 317). HIV virus leads to detrimental effects on the levels and proportion of these cells in the lymphoid tissues and blood. Some of the mechanisms that the virus adopts to deplete the number of $CD4^+$ lymphocytes include dysregulation of cellular proliferation and homeostasis. HIV-1 infection profoundly alters CD4+ T-cells homeostasis, which is the balance between rate of production and cell death.

This leads to a higher rate of cell destruction compared to production, which contribute to the continuous depletion of CD4+ T-cells (Venkataramana, 2013, 18). HIV infection also impairs the cellular production of thymic and hematopoietic progentor cells, which includes inducing cell death through release of the viral proteins gp120.

Another mechanism employed by HIV virus is destroying the integrity of the gastrointestinal (GI) tract's mucosal surface. The local bacterial invasion that occurs across the damaged epithelial lining may lead to microbial invasion, where bacteria such as endotoxin lipopolysaccharide (LPS) trigger systemic immune activation. Such stimulated immune responses may further activate and increase the levels of T-cells and pro-inflammatory cytokines like IL-6 and TNF-alpha that may serve as additional targets that augment the viruses' replication.

2.3.2 Immune Activation

A unique feature associated with HIV infection is the abnormal persistence of immune activation during specifically during the chronic stage (Luckheeram, Zhou, Verma & Xia, 2012, 28).

Abnormal Immune activation is manifested through three key mechanisms that include:

1) High presence of T-cells that exhibit memory phenotype and activation markers;
2) Increase in the number of T and B lymphocytes cells' deaths;
3) The high release of pro-inflammatory cytokines.

The idea that immune activation contributed to the pathogenesis of HIV emerged few years following the discovery of the disease, where CD8+ T-cell activation markers were considered predictor of disease progression (Appay & Sauce, 2008, 45). Nevertheless, the physiological processes underlying the relationship still remains poorly understood. Moreno (2014, 306) also underlines that the link between pathogenesis and immune activation is further exemplified in simian immunodeficiency virus (SIV), which is a virus that infects a species of monkeys (Sooty mangabey and African green monkey).

There is close association between the SIV virus of primates and human HIV virus. The study of SIV and its relationship with chimpanzees offers great promise to understanding HIV-1 pathogenic mechanisms. SIV-infected macaque monkeys exhibit similar characteristics to humans that include rapid $CD4^+$ T-cell depletion and persistent immune and T-cell activation, and finally succumbing to AIDS (Kwantwi, 2017, 76). This is in contrast to African green monkeys show little evidence of immune activation, record normal T-cells counts and do not develop AIDS. This confirms the hypothesis that high immune activation is manifested in the ongoing T cells destruction and proliferation, thus exhausting the immune systems regenerative capacity.

2.3.3 Causes and Consequences of Immune Activation

2.3.3.1 Causes of Immune Activation

Immune activation in HIV-1 infection include an inflammatory response interceded by specific HIV immune response and homeostatatic response from death of CD4 lymphocytes. According to Brenchley et al. (2006, 57), the major causes of immune activation include:

i. Repetitive antigenic stimulation that arises from HIV viral load.

Subsequently, this initiates the activation of the innate and adaptive immunity that attempts to clear the virus.

ii. Direct immune stimulation from HIV gene products such as gp120 or guanine nucleotide exchange factor (GEF)

This leads to activation of macrophages and lymphocytes, which further induces the release of chemokines and pro-inflammatory cytokines (Stebbing, Gazzard & Douek, 2004, 85).

iii. Microbial translocation that arises from increased permeability of the gut mucosa-

This leads to an increase in the levels of bacteria such as LPS. Such microbial products may promote enhanced immune activation of $CD8^+$ and $CD4^+$ T cells; and activation of pro-inflammatory cytokines such as interleukin 1 (IL-2) and tumor necrosis factor-alpha (TNF-α). These cells further stimulate the production of virions.

iv. Another cause of immune response arises from co-infection from other viruses which arises from loss of $CD4^+$ T cells and production of pro-inflammatory cytokines.

This wanes the immune function, thus leading to the loss of control over other pathogens. Accordingly, Chow et al. (2005, 43) justifies the higher levels of immune activation evidenced among individuals with HIV and Hepatitis C co-infections.

v. The imbalance between anti- and pro-inflammatory cells such as loss of the T_H17/Treg cell ratio.

Though O'Connell, Bailey and Blankson (2009, 97) underline that Treg (T regulatory) cells play a vital role in down regulation of immune responses, they might contribute to harmful effects from down regulation of immune activation of specific HIV responses. The imbalance between the two types of cells has been associated with high immune activation levels and disease progression in HIV and SIV related infections.

vi. Discharge of pro-inflammatory cytokines during HIV-infection such as IL-1 alpha, IL-6 and TNF-alpha

These cytokines also refuel immune activation by inducing the activation and differentiation of T-cells (Schuerwegh et al., 2003, 79). Though Interferon-alpha (IFN-α) plays a key role in immunopathogenessis of HIV, it however promotes the hyper-activation of the immune system and destruction of the lymph node.

2.3.3.2 Consequences of Immune Activation

In absence of antiretroviral treatment, continuous inflammation and immune activation leads to detrimental effects on the health and immune system of an individual. Some of the effects include:

a) The increased destruction of $CD4^+$ T-cells

HIV infection leads to a vicious cycle that involves immune activation and death, which subsequently promote replication of HIV (Chadha et al., 2013, 114). This leads to elevated levels of activation and death of $CD4^+$ T-cells.

b) Immune activation also leads to premature T-cell exhaustion and the gradual deterioration of the immune system similar to that of aging.

According to De Biasi et al. (2011, 96), individuals infected with HIV exhibit similar immunological characteristics to those of elderly non-infected HIV persons. Aging is associated with a reduction in T-cells renewal in a process which is referred to as immunosenescence (Klatt, 2016, 29). This can lead to clinical immunodeficiency, which refers to increased risk of the progression of multiple infectious diseases such as cancers.

2.4 Markers of HIV disease progression into AIDS

Over the years clinicians have used many laboratory and clinical markers to estimate the rate of disease progression in HIV-progression, though many other predictive factors remain unknown. Current research has focused on different facets involves in HIV pathogenesis including possible predictive factors such as virological, immunological and host genetic factors of the host (Venkataramana, 2013, 95). Despite the increased usage of antiretroviral therapy in the control of HIV infection, most people still experience side effects.

2.4.1 Viral Markers

a) HIV-RNA

Levels of plasma viral load and $CD4^+$ T-cells have remained the strongest markers to monitor HIV infection (Kanekar, 2010; Gupta & Gupta, 2004). In particular, Klatt (2018, 95) reiterates that the levels of HIV-1 RNA in peripheral blood remain the best laboratory measure to assess progression of AIDS. This is because the marker can be used to predict progression independent of age and levels of $CD4^+$ T-cells (Torres & Lewis, 2014). An inverse relationship exists between the levels of plasma viral RNA and $CD4^+$ T-cell count, where HIV-RNA levels can be used to predict the progression of the disease and rate of $CD4^+$ T-cells depletion. In the acute phase following HIV infection, HIV-1 RNA plasma levels exceed 10,000 copies/ $mm.^3$. Alongside, given that viral mutation of the HIV-1 virus leads to the co-existence of multiple variants in the body of the infected host, these variants have also been utilized by researchers to explain differences in HIV progressions amongst different people.

b) The HIV-1 co-receptors: CCR5 and CXCR4

Majority of HIV-1 variants evidence preferential binding to a particular co-receptor, in what is referred to as HIV tropism. Though there are over 14 chemokine receptors that can act as co-receptors for HIV-1 entry, CCR5 and CXCR4 act as the main co-receptors for HIV-1 infection (Koning, van Rij & Schuitemaker, 2002; Moreno, 2014). Current research has established that greater preference for each of the receptors is associated with distinct rates of disease progression. Some researchers have found evidence that the presence of chemokine receptor variants such as CCR5Δ32 (CCR5 delta32) to have a higher HIV infection resistance (Barmania & Pepper, 2013; An & Winkler, 2010, 49). Therefore, they have hypothesized that the presence of CCR5 delta32 plays a critical role in slowing down the progression of HIV.

Alongside, studies by Ho et al., (2005, 49) and Fatkenheuer et al., (2005) have also evidenced that “X4 variants” showing preference for CXCR4 contribute to higher levels of immunological and clinical deterioration. Compelling evidence supporting the role of CCR5Δ32 in slowing disease progression has prompted development of antiretroviral therapies targeted at CCR5. Nevertheless, Langford, Ananworanich and Cooper (2007, 45) highlight that current evidence on the particular effects of chemokine receptor preference remains contradictory and therefore lack significant clinical value in establishing rate of disease progress.

c) Viral Fitness

Moreno (2014, 59) defines fitness as the replicative adaptability of an organism in a specific environment that is dependent on multiple factors especially arising from immune pressure from the host. Following HIV-1 virus infection, the infecting

virus is exposed to multiple obstacles that it must overcome in order to survive. Some of the obstacles that the HIV virus is exposed to from the host include target-cells availability, concentration of co-receptors like CCR5 and CXCR4, cytotoxic T lymphocytes, administration of ARV, cytotoxic T lymphocytes and the activity of natural killer (NK) cells (Barbour & Grant, 2005, 87). Given that all these factors attempt to limit spread of the HIV virus, its viral fitness is dependent on its ability to adapt to the host by overcoming its replicative capacity (RC).

Nevertheless, HIV-1 is able to adapt to such obstacles through the use of three major mechanisms of viral diversification:

1) Its ability to mutate rapidly arising from the high error-rate of the reverse transcriptase enzyme
2) Recombination of genetically different HIV-1 subtypes that can resist ARV treatment
3) Ability to partially inhibit the host cytidine deaminase APOBEC3G, which is an intracellular anti-viral factor with the ability to inhibit HIV (Klatt, 2016, 99).

Numerous studies have attempted to demonstrate the significance of HIV replicative capacity or viral fitness as an independent marker in progression of the disease.

- Isolates of HIV-1 from long-term survivor patients were found to be less fit compared to those with a high rate of progression (Wright et al., 2011, 114).
- The replicative capacity of the virus was observed to correlate with the rate of CD4+ T-cells decrease over the first 3 years, further suggesting

that replicative capacity may act as an independent progression marker (Prince et al., 2012, 65).

- Virus-specific Cytotoxic T lymphocytes (CTLs) escape mutations have also been evidenced to play a major role in the progression of the disease. Studies by Crawford et al. (2009) and Yue et al. (2009) were able to associate CTL-escape mutations to high levels of viremia experienced in the acute phase of infection

Though these studies suggest that the fitness of a HIV virus is a key determinant influencing the pathogenesis and progression of the disease, research into the actual contributions of replicative capability on disease progression remains largely unexplored (Moreno, 2014, 37).

Other viral factors such as high mutation rate that lead to emergence of drug resistant variants have also been reported to also play a role in influencing the replicative capacity of the virus, and thus having significant influences on HIV pathogenesis and disease progression. In a research survey tracking the pathogenesis of the HIV disease among a cohort of infected individuals in the Netherlands, Gali et al. (2007, 92) reported of increased viral fitness of the virus arising from various adaptation mechanisms such as rapid mutations in the viral gene.

d) HIV in dendritic cells

Dendritic Cells are among the first set of cells that HIV-1 encounters during transmission. While they are capable of capturing and degrading the virus**,** van Montfort et al., (2007, 37) reported that DCs were capable of re-activating neutralized HIV-1 that utilize the cells for passage. Another study also evidenced that HIV-1 transmitted via Dendritic Cells expressed higher X4 tropic strains

compared to R5 strains. Therefore, researchers have theorized that X4-using HIV viruses are transmitted more efficiently via DCs compared to R5 strains, further predicting the roles of the cells in disease transmission and progression (van Montfort, Pollakis & Paxton, 2008; Martin et al., 2004).

2.4.2 Host factors involved in HIV Pathogenesis

As reiterated in the previous sections, the variability that is exhibited in the course of HIV infection is driven by the interplay between viral and host factors. In particular, Moreno (2014, 57) underlines that host factors encompass a multitude of determinants that range from the immune system, human genetics and social or epidemiological characteristics.

Host genetics have been described by Chatterjee (2010, 75) to have an impact on the infection and rate of progression in two distinctive ways that include:

i. Cell-viron fusion that is influenced by CXCR4 and CCCR5 chemokine co-receptors
ii. The immune response of the host that is moderated by Human Leukocyte Antigen (HLA) molecules

- CXCR4 and CCCR5 chemokine co-receptors

There exists enough evidence suggesting the role of genetic polymorphisms within viral co-receptors on HIV disease progression with particular focus on CCR5 and CXCR4 chemokine receptors. Variants of CCR5 delta 32 deletion co-receptors among infected patients have been identified to play a critical role in slowing the progress of HIV to AIDS by reducing rate of viral replication (van Montfort, Pollakis & Paxton, 2008, 77).

Nevertheless, the application of genetic biomarkers in the prediction of disease progression has presented mixed evidence. An international meta-analysis study conducted by Ioannidis et al. (2003, 377) that sought to assess the influence of CCR5 delta 32 alleles on the progression of disease among pediatric cohorts identified that they provided no protection in the long term. Nevertheless, a different meta-analysis involving adult population evidenced that CCR5 delta 32 alleles decreased the rate of progression of HIV and mortality of individuals Loannidis et al. (2001, 55).

- Human Leukocyte Antigen (HLA)

HLA molecules offer the mechanisms that allow the immune system to generate pathogen-specific responses. HLA alleles have also been recognized for their ability to reduce risk for infection by binding. According to Moreno 2014, HLA class 1 genes have demonstrated the strongest association to disease progression and have thus been the center of attention for most researchers. HIV infected individuals exhibiting HLA alleles such as B*5701, B27, B*5703, B51 and B*5801 have been evidenced to experience delayed disease progression to AIDS and better viral control (Klatt 2018). In retrospect, HLA class I genes such as HLA-B35, A 29 and B22 have been associated with rapid progression to AIDS.

2.4.3 Immunological responses and Markers of HIV-1 Infection

Identification of the unique mechanisms that immune activation and chronic inflammation contribute to the progression of HIV disease, independent of HIV RNA level and number of CD4+ T cells has received considerable attention from researchers (Guerra, 2014, 14). Conclusive evidence exists to suggest the role played by the adaptive and innate immune response in the pathogenesis and progression of HIV-1 disease. As highlighted by Leeansyah, Malone and

Sandberg (2013, 8), the molecular and cellular changes that occur as a result of the interactions between the immune responses and viral replication can act as useful biomarkers to inform on the course of infection or predict progression of the disease.

In particular, given that the regulation of the innate and adaptive immune response is achieved through the production of chemokines, soluble cytokine receptors and cytokines, these proteins can act as useful biomarkers that can be correlated to disease progression.

- Innate Immunity

Innate response against HIV comprise of non-specific responses that are developed and passed along from evolution to counter invading pathogens (Brenchley et al., 2016, 49). The major immune-cells populations that have a critical role in innate immunity include natural killer (NK) cells, Dendritic Cells, Type I interferons (IFN), represented by IFN-α and IFN-β. Klatt (2016, 59) identifies that acute HIV-1 infection is characterized by elevated NK cell numbers. In addition, Interferon-γ-induied protein 10 (IP-10) can be biomarker for HIV disease progression, with higher levels predicting lower CD4 lymphocytes counts (Jiao, Zhang & Wang, 2010, 3). Presence of elevated amounts of IFN alpha and IFN beta (IFN-α and IFN-β) in later stages of HIV-infection have been used as a biomarker of increased disease progression (Mothe, Ibarrondo & Brander, 2009, 8).

- Adaptive Immune System

The adaptive immune system responds against specific threats and is thus described as antigen-specific. It is composed of the humoral and cellular immune responses. T-cells acts as the key players in the adaptive immune system where

they mature and differentiate to $CD4^+$ T-cells and $CD8^+$ T-cells (Highleyman, 2010, 9). Thus, existing researches investigating the role of the adaptive immune system on progression of HIV disease have focused on studying specific responses from $CD8^+$ T-cells, $CD4^+$ T-cells and neutralizing antibodies.

- *$CD4^+$ T-cells*

$CD4^+$ T cells are the main helper cells that are involved in the mediation and activation of some of the immune response cells. Mature $CD4^+$ T-cells produce pro-inflammatory cytokines including interleukin-2 (IL-2) that activates the proliferation of T cells. There are five different types of helper T cells that include Th1, Th2, T follicular helper (Tfh), Th17 and regulatory T-cells (Treg).

- *Cytotoxic $CD8^+$ T-cell responses*

The cell-mediated immunity plays a vital role in the regulation of HIV viral replication through the $CD8^+$ T-cell, which are also involved in the production of chemokines and cytokines. Given that $CD8^+$ cell count remain high throughout the infection period, Gupta, V., & Gupta, S. (2004, 18) claim that use of $CD8^+$ cell count as marker is less effficent when compared to $CD4^+$ cell count. Nevertheless, a low CD4/ CD8 ratio has been described to be highly predictive for death arising from AIDS infection (Kiepiela, Smith & Rosenberg, 2005, 95).

- Neutralizing antibodies

The humoral response of the adaptive immunity against HIV includes the release of neutralizing and non-neutralizing antibodies that are directed particularly against the HIV-1 envelope glycoprotein (Env) Richman, D.D., et al. (2003, 44). According to Klatt (2016, 39), most of the HIV viral proteins are highly

immunogenic where they induce antibodies directed against its glycoprotein gp120 and gp41 subunits following infection.

Virus neutralizing antibodies (NAbs) develop over time and are often directly against gp120. Current evidence on the contribution of NAbs on progression of HIV disease is inconclusive where cohort studies have failed to demonstrate critical role of humoral responses on outcome of the disease (Euler et al., 2010; Richman et al., 2003). McMichael (2006, 44) also underlines that a large proportion of initial HIV-related vaccine research had centered on the induction of humoral immunity, specifically on the HIV gp120 envelop protein. Figure 2 below shows the changes in lymphocytes, viral load, binding bodies and neutralizing antibodies as infection progresses.

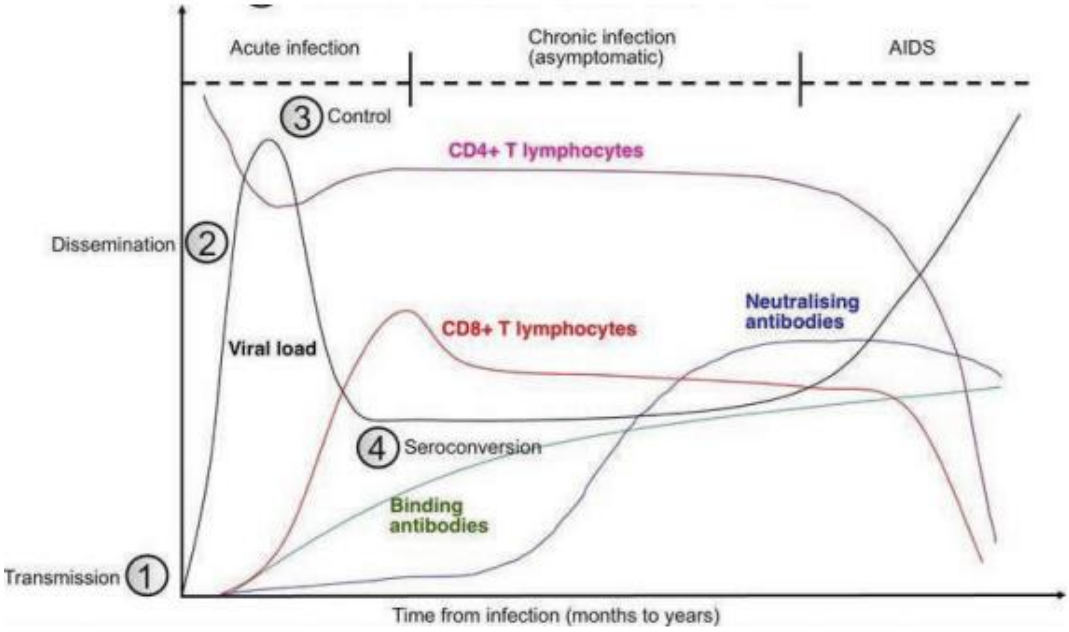

Figure 2 Typical immune response to HIV-1 (Highleyman 2010, 13).

Nevertheless, Moreno 2014 reiterates that the ability of the Env to protect susceptible virus regions from NAbs remains among the major obstacle restricting the development of vaccines. There also exist a large number of other immune-response genes that have also been identified to influence the rate of disease progression, where Chatterjee (2010, 34) claims that they can either have stimulatory, inhibitory or both effects on the replication of HIV.

Surrogate Markers

Accordingly, the detection of antibodies against HIV within the blood such as gp120, gp 41, p24 and p17 have acted as the major serological markers in predicting the clinical course of infection and disease progression.

Several authors have attempted to provide a description of antibodies that qualify as HIV disease surrogate markers:

> *Surrogate markers of HIV infection are, by definition, measurable traits that correlate with development of clinical AIDS that should fulfill the following criteria: (i) permit identification of patients at highest risk of disease progression, (ii) aid in estimating the duration of infection, (iii) assist in disease staging, (iv) predict development of indicator/ opportunistic diseases, and (v) follow, in vitro, the therapeutic efficacy of immunomodulating or antiviral treatments (Tsoukas & Bernard, 1994, 4)*

Other Factors

Age

The elderly people have also been evidenced to be at a higher risk of HIV disease progression and resistance to treatment due to various unique factors that include: (Appay & Sauce, 2008, 41)

(1) Lower T cells count and greater thymic involution or the progressive shrinkage of the thymus. These factors may impair the ability of treatment to recover their $CD4^+$ T cells

(2) Expression of higher numbers of T cell chemokine co-receptor that may further contribute to viral entry into various immune cells

(3) They have a low production of Interleukin-2 that may include a reduction in T-cells renewal, which may lead to immunosenescence or decline in immune response that arises from aging.

Genetic factors such as APOBEC3G and MBL-2 have also been implicated in accelerating disease progression to AIDS in children thus making their progression faster compared to adults (Klatt, 2016).

Gender

A number of studies have evidenced gender variations in levels of HIV-1 RNA levels and rate of progression to AIDS (Langford, Ananworanich, & Cooper, 2007; Donnelly et al., 2005; Sterling et al., 2001, 25). In particular, low levels of $CD4^+$ T cells in women have been associated with higher levels of HIV-RNA compared to men with similar CD4 count.

Conversely, high $CD4^+$ T cells among women have been correlated with lower levels of HIV-RNA compared to men. Differences in the levels of viral load following infection have been noted between men and women, with that of women being 15,103 copies/mL and 50,766 copies/mL for men (Klatt, 2016, 175).

This has been attributed to the difference in immune responses where women express heightened innate immune activation with higher production of interferon-

alpha (Addo & Altfeld, 2014, 177). Sterling et al. (2001, 14)'s study further established that women with equal viral load to that of men have a 1.6-fold higher risk of developing AIDS. However, current research highlight that the biological basis for this variation remains unclear.

The interaction between psychosocial and physical factors have also been evidenced to play a critical role in disease progression which include factors such as depression, denial and stress (Ashton et al., 2005; Leserman et al., 2000).

2.5 Markers for disease progression in resource-limited settings

Current gold standard biomarkers for monitoring the progression of HIV disease include the levels of HIV-RNA and $CD4^+$ T cell count. Nevertheless, Balakrishnan et al., (2011, 823) underlines that though such assays are routinely used in developed nations, their usage in resource-limited regions is restricted from the fact that they require robust laboratory infrastructure and expensive equipment. Considering that the majority of HIV positive patients are located in resource-restrained countries, the use of low-cost and easier to implement alternatives has been suggested.

Given that the progression of the disease is influenced by the synergetic interaction between various immunological, viral and host co-factors, different surrogate markers may also be used to assess disease progression. Markers that have been proposed for uses in such regions include body mass index (BMI), haemoglobin, delayed type hypersensitivity responses (DTH) and total lymphocyte count (TLC) (Langford, Ananworanich & Cooper, 2007; Kwantwi et al., 2017).

- Body Mass Index

Measurement of the body mass index among HIV positive individuals has been recognized to be of critical importance in the management of the disease. According to Kwantwi, L. B. (2017, 53) this is because of the high association between HIV disease and wasting syndrome. The condition involves involuntary and progressive weight loss of greater than 10% that may be accompanied by diarrhoea or fever which is the criterion that the Classification of Disease CDC considers to satisfy AIDS diagnosis. Several researchers have evidenced a high correlation between BMI with response to ARV and disease progression.

Balakrishnan, Solomon and Mayer (2005, 345) research reported rapid decline in BMI 6 months before the onset of AIDs, though the sensitivity of the measure was reported to be 33%. Alongside, baseline. Furthermore, Koethe et al. (2011) study also found a positive correlation between BMI and CD4 count, pre- and post-ARV therapy initiation. CD4 cell-count was reported to increase among patients that had a pretreatment BMI of 25-30 3kg/m^2 and decreased for those with lower or higher BMI levels. Thus, BMI was evidenced to correlate with slower progression to AIDS and individuals' immune constitution. Therefore, the ease associated with measuring the BMI parameter makes it an ideal marker for use in predicting HIV disease progression in resource constrained regions

- Delayed Type Hypersensitivity DTH skin testing

DTH responses are mediated by $CD4^+$ T cells that produce interferon -γ and interleukin-2. DTH testing is a clinical method that can be readily performed *in vivo* to assess immune function by measuring the immunologic reaction to certain antigens. Individuals living with HIV have a reduced DTH responsiveness when

compared to healthy individuals. Minidis, Mesner & Okulicz (2014, 199) reported that while over 90% of healthy persons are non-anergic, or reactive to DTH recall antigens, about 60% of HIV infected patients have non-anergic responses.

It has also been estalished that decline in DTH responses parallels with levels of CD4 cells with subsequent increase in mortality among the patients.Levels of DTH responsiveness among untreated HIV patients have also been reported to be greater among patients with a CD4 cell count of greater than 400 cells/ mL compared to those with lower levels (Obirikorang & Yeboah, 2009, 102).Thus, several reports have evidenced the potential application of DTH test as an independent marker of progression of HIV independent of the level of CD4 cells (Langford, Ananworanich & Cooper, 2007, 12).

- Total lymphocyte count

TLC has also been investigated as a potential alternative marker to CD4+ that can be used in regions with low resources. Nevertheless, Kwantwi et al. 2017 underlines that despite the lack of agreement on the average cut-off for sensitivity, current guidelines from WHO recommend a baseline of 1200 cells /mm3 or below for use as a substitute marker for initiation of ART. Several large-scale studies have also produced consistent results that have correlated TLC levels of less than 1200 cells/mm3 to progression of HIV disease and mortality (Costello et al., 2005, 265). Nevertheless, the correlation between TLC and CD4 levels has been generally poor. While this measure has been validated for use as monitoring progression of the disease, it’s usage for therapeutic monitoring is not recommended.

- Haemoglobin

The level of hemoglobin (Hb) among HIV-infected populations has been evidenced to reflect the rate of disease progression where Hb levels decline with increasing HIV disease progression. According to Kwantwi et al 2017, this measure can be used as an independent prognosis marker irrespective of demographic differences. Decreasing levels of hemoglobin among HIV positive individuals has been attributed to wide array of factors that include bleeding, suppression of bone marrow and the lack of sufficient diet. A positive correlation between the levels of hemoglobin and CD4 count decline has also been established among HIV naïve patients (Costello et al., 2005; Obirikorang & Yeboah, 2009). Shah et al., 2007) underlines that HB levels can act as an independent measurement of prognostic information similar to CD4 count which makes it ideal for use in regions with limited resources.

As access to antiretroviral therapy continues to improve across the globe, it is evident that there is a need to develop low-cost markers of HIV disease progression that are readily accessible.

2.6 HIV/AIDS Management

In addition to the role of viral and host's bio-medical factors on the rapid transition of HIV into AIDs, psychological and social factors have been identified to play an integral role in influencing the ability of an individual to cope with HIV/AIDS. In particular, Rachlis, Mills and Cole (2011) reiterate that health care professionals must consider the influence of factors such as stigma and cultural factors during treatment in order to develop more personalized interventions for patients. These social factors in most cases are reasons why patients don't get adequate treatment hence the progression of HIV to AIDS.

2.6.1 Stigma

Schweitzer, Mizwa & Ross (2010, 118) highlight that stigma is one of the single most important factors that produces and extends negative psychological effects associated with HIV and AIDS among infected individuals. The UNAIDS (2001) defined stigma “an act of identifying, labeling, or attributing undesirable qualities targeted towards those who are perceived as being shamefully different and deviant from the social ideal (Aggleton, 2001, 79).” People living with HIV/AIDs are particularly in Africa discriminated and stigmatized against for a variety of reasons. Onyango-Ochieng (2009, 15) found out that people were irrationally afraid of acquiring the disease from people infected with it and that transmission was considered a violation of social conventions related to proper sexual relationships. Multiple researchers also acknowledge that stigma prevents the majority of infected people from obtaining medical care, adopting preventive measures or seeking counseling, which may lead to faster progression into AIDS (Schweitzer, Mizwa & Ross, 2010; Murray et al., 2004). Despite the fact that most ARV treatments are offered for free in most resource-limited countries, fear of stigmatization can prevent such patients from obtaining those drugs.

Stigmatization does not only affect the individual but the entire family at large which may face violence and rejection from the wider society leading to isolation. As reiterated by Rachlis, Mills and Cole (2011, 93), health care providers must be aware of the stigma that HIV positive patients face and must therefore be scrupulous in protecting their patients’ confidentiality. The authors suggest that health care providers can also attempt to take additional steps to minimize effects of stigma. These include disclosing positive HIV test to close family members of the patient in order to build a support system for the

individual and further educate family members about HIV (Pontali, Vareldzis & Narain, 2003, 59).

2.6.2 Cultural and Religious beliefs

Cultural factors have also been evidenced to influence perceptions about HIV disease, type attitude of HIV positive patients towards ARV drugs and the perceived benefits of such drugs. A research by Schweitzer, Mizwa and Ross (2010, 275) also found out that existential issues such as religious beliefs and spirituality may become of increasing importance to individuals that are diagnosed with HIV disease progression. Despite the significant role that religious and spiritual dimensions may play in the lives of infected populations, the research found out that some religions contributed to further stigmatization. An example is Parker and Aggleton (2003, 374) who claim that some religions have been blamed for advocating the submissive role of women, encouraging women's ignorance to sexual issues as a form of purity and promoting gender inequality in relations. Such sexual and gender stereotypes that are constructed by religion were thus evidenced to play a role in the risk of HIV diagnosis and progression.

Culture has multiple destructive roles that relate to false beliefs related to the treatmet or prevention of HIV/AIDS. Pontali, Vareldzis and Narain (2003, 117) cite widow inheritance as an example of a destructive practice that is prevalent in some African cultures. Widow inheritance refers to the cultural practice where a man is required to inherit the wife of his deseased brother. Though such a tradition is meant to ensure continuous support for the wife and children, they have however been established to contribute to the risk of HIV infection and faster progression of the disease into AIDS. Alongside, Pontali, Vareldzis and Narain (2003, 54) evidenced that clients who hold stringent traditional cultural

beliefs may tend to seek consultation from traditional healers which may subsequently limit their adherence to ARV drugs and access to health facilities.

2.6.3 Social economic Factors and Poverty

Socioeconomic factors explain a substantial proportion of the differences in late access to HIV testing, HIV care, and HIV-related outcomes following ART. Worldwide HIV/AIDS is associated with inequality in health in all age groups underpinned by various cultural, economic and environment factors that are referred to as ‘social determinants’ of health. In high-income countries, differences in mortality rates between HIV-infected people living in Europe and in North America are substantial with higher mortality in socially disadvantaged racial groups than in native white populations, and in women than in men in North America but not in Europe (Klatt, 2016, 116). Such results are explained by differences in socioeconomic status and access to health care.

Poverty has also been underlined to contribute to the progression of the HIV disease. This is evidenced in Rachlis, Mills and Cole (2011, 77) study which highlights that in addition to having the highest prevalence of HIV in the world, Sub-Saharan countries are also among the poorest countries. Poverty was also underlined to limit the abilities of patients to access transport and health facilities which further hampered the medical access and their adherence to ARV drugs (Schweitzer, Mizwa and Ross, 2010, 45). High poverty levels in most regions have also been attributed to lack of access to proper nutrition.

Pontali, Vareldzis and Narain (2003) stated that HIV positive patients living in poverty ridden regions were at higher risk of contracting other infectious diseases that led to higher mortality rates. The effects of poverty levels on low adherence to ARV drugs were also evidenced in two studies based in Kenya and Senegal

(Onyango-Ochieng, 2009; Katzenstein, Laga & Moatti, 2003). In both studies it was evidenced that even in situations where the cost of treatment was free of charge, the inability to access fare still acted as an addition barrier that limited access and acquiring the drugs.

3 METHODOLOGY

3.1 Study Design

The aim of the research paper was to identify the factors that are associated with rapid progression of HIV disease from infection to the AIDS stage in developing countries. To achieve this, a systematic search and review methodology was identified as the most appropriate strategic approach. The University of York's Centre for Reviews and Dissemination (2009, 39) underline the systematic reviews are particularly useful in health-care based researches for various reasons. Firstly, health care decisions for public policy and individual patients require the use of latest and best available research. Nevertheless, achieving this can be difficult as a result of the extensive and diverse amounts of data that is produced by individual studies, which can be methodologically flawed, biased or misrepresented. Alongside, the conflicting results generated by individual studies make it difficult for health care practitioners to identify the most reliable findings that can serve as a basis for decision-making.

Systematic reviews, therefore, aim to overcome such challenges through the identification and evaluation of findings from relevant individual studies. A systematic review has been defined as:

"A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (ten Ham-Baloyi & Jordan, 2016, 5).

The aim of the present review was to synthesis findings from a wide array of scholarly research to develop definitive findings and gain new understanding on the subject matter. As highlighted by Moher et al., (2009, 54), the ability of

systematic reviews to combine different studies enhances the reliability of the results compared to those derived from the use of a single study. This allows the formulation of evidence-based nursing practices that have been derived from robust research studies of the highest quality.

The University of York's Centre for Reviews and Dissemination further highlights that good review should include a well-defined question that includes election of appropriate methods of answering the question. The review should also include a comprehensive search using appropriate and clear criteria to reject or select studies. The guidelines also highlight the need to document the process of extracting sources, assessing their quality and synthesizing data obtained from the studies.

3.2 Systematic literature search

The search for relevant scientific journals was guided by the question:

"What research studies are available that identify the factors influencing the rate of HIV progression to AIDS in developing countries?"

A three-stage process of literature searching was undertaken that included electronic databases, use of follow-up references, citation searching and manual searching in the school's library. These included searching for electronic databases such as the Cochrane library databases, PsychInfo, PubMed, JSTOR, EBSCO and the Journal of the International AIDS Society (JIAS). The use follow-up references entailed the process of using key paper retrieved from these databases to identify appropriate articles that have been cited in the review and meet our criteria. The approach allowed the identification of clusters of related and highly relevant, papers to inform our study.

Some of the search terms included “HIV-AIDS progression,” “Virological factors,” “Immunological factors,” “Host factors,” and “Resource limited settings.” To identify as many relevant studies as possible, the second search strategy also included the use of methodological filters. According to Wong et al, (2006, 57), these are key words that are added or combined with the search terms of a subject in order to increase the likelihood of extracting the most appropriate studies. Some of the terms that were utilized in the detailed search strategy include:

(‘Rate of progression’ OR ‘faster progression’ OR ‘Rapid progression’) AND (‘virological factors’, ‘host factors’, ‘immunological factors’) AND (HIV-AIDS) AND (‘developing countries’).

The inclusion and exclusion criteria were used to evaluate the eligibility of the results.

3.3 Exclusion & Inclusion Criteria

The articles that were considered for the study were those that focused on the study of virological, host or immunological factors that contributed to high rate of HIV disease progression. To be eligible, articles also needed to have been focusing on in resource-poor settings and published in English between 2010-2018. Only peer reviewed journals, reports and conference papers we considered for the study. Studies that were published earlier than 2010 and not based in developing countries were excluded. Papers that were not peer reviewed were also not included in review such as news reports, editorials or commentaries Reports that focused on the risk of HIV infection, prevention or transmission were also excluded.

The systematic literature search described above produced a total record of 685. After screening of titles and abstracts of 56 articles, 23 were identified to be of relevance to our research question and full papers were obtained for detailed assessment. A total of 9 articles that met our inclusion criteria were selected for the final review. The major causes for exclusion included the use of less than 50 cohorts of HIV positive patients, a short follow up period and narrow focus on predictors of HIV progression.

Venkataramana (2013, 25) was the only review article that was identified for the study. With particular focus on developing countries, the study attempted to offer an analysis of alternative markers that may be used for disease progression. Some of the markers that were considered for analysis included CD8 counts, hemoglobin and Total Leukocyte count. From the results, the author identified a significant positive correlation between CD4 ells and haemoglobin levels, CD8+T-cell counts ad TLC. Kwantwi (2016, 352) cross sectional case control study in Ghana also identified the role of haemoglobin as a potential marker that influence HIV disease progression.

Majority of the studies included for review were retrospective studies that relied on clinical data as identified in Table 3 above (Pantazis et al., 2012; Huang et al., 2011; Chadha et al., 2013; Guerra, 2014; Mackelprang et al., 2015; Jiang et al., 2013; Gadpayle et al., 2010). The only cross-sectional case control study was from Kwantwi (2016, 116), undertaken in Ghana among 192 patients. Two studies focused exclusively on the study of the influence of age, transmission mode, gender and drug usage on progression of HIV disease. The first article from Jiang et al. (2013, 34) was based on clinical data of 691 patients from China. Age at diagnosis educational level and modes of transmission were correlated with progression of HIV to AIDS, while gender was not identified to

influence progression to AIDS. HIV infection at older age was identified to increase the risk of developing AIDS. Among the various transmission categories, introvenous drug users were also evidenced to have a slow progression rate compared to homosexual men.

Gadpayle et al. (2010, 114) study was based in India, and involved analysis of data from 344 patients. Results from the study indicated that progression to AIDS among drug users was higher compared to transmission of AIDS of heterosexual. Age during seroconversion was identified to be the strongest demographic factors that influenced progression rate. Children that acquired HIV in the fetus were identified o have a rapid progression rate compared to ones infected after birth. Sex of the patients had no significant influence on the rate of progression. Three articles focused on evaluating the impacts of viral factors and hosts' immunological response on rate of disease progression (Mackelprang et al., 2015; Huang et al., 2011) Guerra, 2014).

Mackelprang et al. (2015, 16) study was based on data of 510 HIV positive couples in Sub-Saharan Africa. The aim of the study was to model the effects of the source partner and host partners on HIV-1 set point and rate of progression. Findings from the study evidenced that the variation in HIV-1 seroconverter set point between couples could be explained by hosts genetic and source partners characteristics. In particular, hosts' HLA alleles and the levels of HIV-1 RNA levels in the transmitting partner were evidenced to account for 46% of the variability in plasma HIV-1 RNA set point.

Huang et al. (2011, 28) study in South Africa reported that high viral replication capacity of HIV-1 was associated with low CD4 cells and high progression to AIDS. Guerra (2014, 53) study in Zambia also sought to identify the effects of viral replicative capacity on disease progression and the use of immune

activation as a predictor of disease progression. Results identified that low viral replicative capacity of the virus was associated with minimized loss of CD4 cells and delayed progression to AIDS. Chronic immune activation was identified as a predictor of disease progression that correlated with viral replicative capacity. Pantazis et al. (2012, 35) study focused primarily on the difference in the rate of disease progression and infection from opportunistic infection between South Africans and Europeans. South Africa cohorts were identified to have a slower rate of CD4 cell depletion, though presented higher probability of being diagnosed with AIDS. This was identified to arise from co-infection with other diseases such as Tuberculosis.

4 FINDINGS

The variability experienced in the clinical course of HIV disease has been attributed to a multitude of risk factors that include host, viral and immunological co-factors. While the majority of existing literature focuses on the analysis of populations in developed countries, the review was undertaken to identify studies focusing on HIV progression variability in resource-poor countries. Current evidence suggests that differences in demographic, education, social, cultural and economic factors between developed and developing countries may contribute to variability in the rate of HIV disease progression. The following section offers a broader discussion on the results obtained from the nine studies that met the inclusion criteria of this review.

4.1 Old Age

Age at seroconversion was consistently identified to be among the most influential factors in the rate of disease progression. Studies from Jiang et al. (2013, 225) and Chadha et al. (2013, 15) established a strong correlation between old age and higher rate of disease progression among populations living in low-resource regions of Africa, India and China. These findings are congruent to those undertaken in developed countries, which have also attributed older age to rapid HIV-AIDS progression (Appay & Sauce, 2008; Mussini et al., 2015, 77). In particular, the low levels of CD4 cell count associated with older age arise from the continuous deterioration of thymic function. Thus, the capacity of older subjects to generate new CD4 cells in response to increased depletion from the HIV virion is decreased leading to deteriorated immune response.

4.2 Racial Variation

Previous studies on the influence of racial variation on the amount of CD4 cell counts and viral loads have produced inconsistent results due to inability to exclude co-founders (Herbeck, et al., 2012, 36). However, results from Pantazis et al. (2012, 48) research that compared cohorts from South Africa and Europeans evidenced milder differences in CD4 count. Cohorts from Africa were evidenced to have lower levels of CD4 cells at seroconversion, which was accompanied by slower rate of CD4 cell depletion. The slow decline in the rate of CD4 cells among Africans, therefore, did not confer any advantages to them. They were documented to reach similar levels of CD4 count to Europeans within 2.5 years, where their survival rates were thus similar.

The slower rates of CD4 cell count among Africans have also been reported in studies based in France (Lewden et al., 2010; Meyer, Chaix & Nagy, 2007). This variability has been attributed to a variety of factors that include the environmental and genetics. Lewden et al., (2010, 35) explained that the genetic factors that may explain this variation include the segregation of HLA alleles among African groups. Lovvorn et al. (2010, 114) also expounded that that difference in environmental factors between Europe and Africa could contribute to this variation. The high prevalence of environmental factors such as respiratory and parasitic co-morbidities has been postulated to play a role in influencing immune status of cohorts. In line with previous studies the present review underlines that race does influence the rate of progression independently of other co-founders such as access to care and psychological factors.

4.3 Co-Infections

Co-infections have been well documented to contribute in the pathogenesis of the HIV virion, subsequently leading to increased viral load among HIV-positive patients. In our current study, Venkataramana (2013) and Pantazis et al. (2012) evidenced that one of the factors that has influenced higher progression of HIV among individuals in resource-poor setting is TB co-infection. M tuberculosis has been evidenced to be among the most prevalent co-infecting pathogens among Africans and other low-income countries (Moreno, 2014, 154). Compelling evidence exist to suggest the role of co-infections on the activation of immune response, which further enhances the replication of the HIV virus. Pantazis et al. (2012) study further matched this observation among South Africans, where TB was the most common co-infection associated with this cohort, followed by HIV wasting syndrome.

Co-infection with TB was associated to rapid progression of HIV in resource-poor setting in Africa, despite having a slower CD4 cell loss. Furthermore, review from Torresc and Lewis (2014, 54) underlined that HIV-TB co-infection enhances the rate of disease progression by altering the levels of cytokines, which led to the premature death of patients. These results are in agreement with a previous study conducted by Bakanda et al. (2010, 34) on the role of malaria co-infection on disease progression. The authors found out that malaria facilitated HIV replication by increasing immune cell activation and increased production of cytokines. Consequently, this leads to increased rate of CD4 cell loss and higher risk of AIDs diagnosis.

4.4 Markers of disease progression

The present review identified the increased need to identify new markers of disease progression that are easy to use and less costly to ones used to monitor CD4 levels and viral load in developed countries (Venkataramana, 2013, 36). The introduction of advanced and sensitive assay technologies has offered clinicians with the ability to quantify a wide array of soluble biomarkers. Therefore, investigators are able to simultaneously study numerous inflammatory profiles than before. The markers that have been identified to present highest potential for use as predictors of disease in developing countries include hemoglobin levels, neopterin and Total Leucocyte Count (Kwantwi, 2016, 3).

A wide selection of previous literature has also highlighted that changes in haemotological functions accompanying HIV infection can act as surrogate markers to predict HIV progression and CD4 count. The influence of host factors such as HLA alleles and gender on viral load set point was also documented by Mackelprang et al. (2015, 3), which reflect findings from prior studies by Shah et al (2007, 41) and Euler et al. (2010, 164). The study from Chadha et al. (2013, 34) also supported the findings that low levels of CD4 T cells were most predictive of early progression of HIV infection. Consistent with suggestions from WHO on the diagnosis of AIDS, levels of CD4 cells below 200 cells cubic millimeter were evidenced to indicate increased risk of AIDS onset in developing countries.

4.5 Health Determinants

The role of determinants of health has also been exemplified to play a critical role in influencing risk of HIV infection and progression in resource poor countries. These health determinants have been underlined to influence the HIV

patients' quality of life, their adherence to treatment and mortality (Huang et al., 2011, 44). In particular, previous studies from Silva et al. 2010 and Leserman (2008) reinforced the effects of socio-economic factors on adherence and access to treatment. The failure to adhere to antiretroviral treatment has also been associated with increased risk of drug resistance. In addition to increasing rate of disease progression, resistance to such drugs has been evidenced to limit the treatments options and risk of transferring the resistant virus to other hosts (Perno et al., 2008, 21).

Progression of HIV to AIDS has been shown to be faster in among populations with lower levels of education. Higher level of education level was identified to act as a preventative factor associated with slower HIV to AIDS progression in studies from both developed and developing countries (Huang et al., 2011, 33). Some of the ways that education has been evidenced to slow progression rate include the capacity and know-how to comply with complex ARV medications. This is consistent with our findings where Gao et al., (2010, 65) and Monge et al., (2012, 71), have correlated higher adherence to drugs among populations with higher education levels.

Alongside, education has been attributed to higher socio-economic status and enhanced abilities to overcome stress that may be associated with HIV infection (Damtie, Yismaw & Anagaw, 2013, 35). Other common health determinants that may influence progression include stigma, culture, low-income and access to care. Low socio-economic status in developing countries have also been highlighted by Klatt (2016, 34) to influence the rate of disease progression by having a synergic effect on the development of immune system of children.

4.6 Immune Activation

Chronic immune activation is underlined to be a vital determinant of disease progression, where persistent immune activation has been identified as one of the hallmarks of HIV infection. The present review evidences the role of immune activation as a potential predictor of disease of disease progression (Kwantwi, 2017; Guerra 2014, 43). In particular, the study by Kwantwi (2017, 33) in Ghana evidenced widespread dysfunction of T-cells and hyper activation of chronic B-cells. The study found out that during the first year of infection, there was considerable increase in levels of markers of T-cell activation such as sCD27. Alongside, Guerra (2014, 116) further observed that higher CD8 T cell activation in the Zambian cohort was associated with rapid rate of CD4 loss, which mirrors observations from Hunt, et al. (2010, 33). This is consistent with previous research from Highleyman (2010, 21) which noted that heightened immune activate is a reliable marker of progression as compared to viral load. The researcher suggested that local immune activation offered an advantage to the HIV virus inducing it, by increasing the amounts of target cells that were susceptible to the virus.

4.7 Injecting Drug Users

There have theoretical concerns of the effects of injecting drug use on the progression of HIV disease, where early *in vitro* studies (Coutinho, 1991, 25) suggest increased replication of HIV from drugs such as opioids. Nevertheless, clinical studies have often produced inconsistent results. The study from Wood et al., (2008, 122) identified that after initiation of HAART, the mortality rate of intravenous drug users IDU) was similar to that of non-IDU. In retrospect, a study by the Antiretroviral Therapy Cohort Collaboration (2008, 116) produced completely different results, where HIV positive IDUs expressed lower

life expectation compared to the other groups. Gadpyle et al. (2012, 52) attributed drug use to low access to care and lack of adherence to medication. In particular, intravenous drug use at old age was linked to increased rate of HIV progression and mortality.

5 CONCLUSIONS

As access to antiretroviral therapy continues to improve across the globe, it is evident that there is a need to develop low-cost markers of HIV disease progression that are readily accessible. Current gold standard biomarkers for monitoring the progression of HIV disease include the levels of HIV-RNA and $CD4^+$ T cell count. Nevertheless, such assays are routinely used in developed nations; where their usage in resource-limited regions is restricted from the fact that they require robust laboratory infrastructure and expensive equipment. The limited healthcare infrastructure of most developing countries and minimal access to such facilities has also been evidenced to play a role in influencing the health outcomes of these groups. Considering that the majority of HIV positive individuals are located in resource-restrained countries, the use of low-cost and easier to implement alternatives has been suggested.

In particular, given that the progression of the disease is influenced by the synergetic interaction between various immunological, viral and host co-factors, different surrogate markers may also be used to assess disease progression. The present review identified the increased need to identify new markers of disease progression that are easy to use and less costly to ones used to monitor CD4 levels and viral load in developed countries. The introduction of advanced and sensitive assay technologies has offered clinicians the ability to quantify a wide array of soluble biomarkers. Therefore, investigators are able to simultaneously study numerous inflammatory profiles than before. The findings from the research also reiterated that a clear underrating of the variability in progression of HIV infection is vital in nursing research in order to guide clinical management, treatment strategies and counseling prevention.

In addition to viral and hosts' biological factors, the spread and progression of HIV disease is also attributed to a wide range of factors that include behavioral, access to health services, social support and socio-economic factors. Therefore, in order for nurse practitioners to design effective intervention and prevention programs, it is vital to consider social and cultural variations between individuals. Clinicians should also demonstrate expertise and skills not only in offering the most appropriate intervention but also in their individual beliefs and attitudes related to the cultural context of a HIV positive patient. The health beliefs of individual patients, their behaviors, perceptions and traditional values should thus

be prioritized upon during the development of appropriate and personalized interventions for patients. Alongside, practitioners can also include services such as offering supportive counseling to patients and their caregivers in order to minimize the stress associated with stigma.

LIST OF REFERENCES

Aggleton, P. 2001. *Comparative analysis: research studies from India and Uganda. HIV and AIDS-related discrimination stigmatization and denial*. Revised.

An, P., & Winkler, C. A. 2010. Host genes associated with HIV/AIDS: advances in gene discovery. *Trends in genetics*, *26*(3), 119-131.

Antiretroviral Therapy Cohort Collaboration. 2008. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *The Lancet*, *372*(9635), 293-299.

Appay, V., & Sauce, D. 2008. Immune activation and inflammation in HIV-1 infection: causes and consequences. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, *214*(2), 231-241.

Ashton, E., Vosvick, M., Chesney, M., Gore-Felton, C., Koopman, C., O'shea, K., ... & Spiegel, D. 2005. Social support and maladaptive coping as predictors of the change in physical health symptoms among persons living with HIV/AIDS. *AIDS Patient Care & STDs*, *19*(9), 587-598.

Bakanda, C., Birungi, J., Mwesigwa, R., Ford, N., Cooper, C. L., Au-Yeung, C., ... & Dybul, M. 2011. Association of aging and survival in a large HIV-infected cohort on antiretroviral therapy. *Aids*, *25*(5), 701-705.

Balakrishnan, P., Iqbal, H. S., Shanmugham, S., Mohanakrishnan, J., Solomon, S. S., Mayer, K. H., & Solomon, S. 2011. Low-cost assays for monitoring HIV infected individuals in resource-limited settings. *The Indian journal of medical research*, *134*(6), 823.

Balakrishnan, P., Solomon, S., Kumarasamy, N., & Mayer, K. H. 2005. Low-cost monitoring of HIV infected individuals on highly active antiretroviral therapy (HAART) in developing countries. *Indian J Med Res*, *121*(4), 345-355.

Barbour, J. D., & Grant, R. M. 2005. The role of viral fitness in HIV pathogenesis. *Current HIV/AIDS Reports*, *2*(1), 29-34.

Barmania, F., & Pepper, M. S. 2013. CC chemokine receptor type five (CCR5): an emerging target for the control of HIV infection. *Applied & translational genomics*, *2*, 3-16.

Brenchley, J. M., Price, D. A., Schacker, T. W., Asher, T. E., Silvestri, G., Rao, S., ... & Blazar, B. R. 2006. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature medicine*, *12*(12), 1365.

Buggert, M., Frederiksen, J., Noyan, K., Svärd, J., Barqasho, B., Sönnerborg, A., ... & Karlsson, A. C. 2014. Multiparametric bioinformatics distinguish the CD4/CD8 ratio as a suitable laboratory predictor of combined T cell pathogenesis in HIV infection. *The Journal of Immunology*, 1302596.

Celentano, D. D., Galai, N., Sethi, A. K., Shah, N. G., Strathdee, S. A., Vlahov, D., & Gallant, J. E. 2001. Time to initiating highly active antiretroviral therapy among HIV-infected injection drug users. *Aids*, *15*(13), 1707-1715.

Chadha, S., Bhalla, P., Jha, A. K., Gautam, H., Saini, S., Anuradha, S., & Dewan, R. 2013. Disease progression and antiretroviral therapy in newly seropositive HIV subjects in a tertiary care hospital in North India. *The Journal of Infection in Developing Countries*, *7*(02), 110-115.

Chatterjee, K. 2010. Host genetic factors in susceptibility to HIV-1 infection and progression to AIDS. *Journal of genetics*, *89*(1), 109-116.

Chow, K. Y., Ang, L. W., Verghesse, I., Chew, S. K., & Leo, Y. S. 2005. Measurable predictive factors for progression to AIDS among HIV-infected patients in Singapore. *Ann Acad Med Singapore*, *34*(1), 84-89.

Coutinho, R. A. 1991. Frequent injecting impairs lymphocyte reactivity. *Aids*, *5*(1), 35-41.

Crawford, H., Lumm, W., Leslie, A., Schaefer, M., Boeras, D., Prado, J. G., ... & Gilmour, J. 2009. Evolution of HLA-B* 5703 HIV-1 escape mutations in HLA-B* 5703–positive individuals and their transmission recipients. *Journal of Experimental Medicine*, *206*(4), 909-921.

Damtie, D., Yismaw, G. & Anagaw, B. 2013. Common opportunistic infections and their CD4 cell correlates among HIV-infected patients attending at antiretroviral therapy clinic of Gondar University Hospital, Northwest Ethiopia. *BMC Research Notes*, *6*(1), 534.

De Biasi, S., Pinti, M., Nasi, M., Gibellini, L., Bertoncelli, L., Manzini, S., ... & Cossarizza, A. 2011. HIV-1 infection and the aging of the immune system: facts, similarities and perspectives. *Journal of Experimental & Clinical Medicine*, *3*(4), 143-150.

Euler, Z., et al. 2010. Cross-reactive neutralizing humoral immunity does not protect from HIV type 1 disease progression. J Infect Dis, 201(7): 1045-53

Fanales-Belasio, E., Raimondo, M., Suligoi, B., & Buttò, S. 2010. HIV virology and pathogenetic mechanisms of infection: a brief overview. *Annali dell'Istituto superiore di sanita*, *46*, 5-14.

Fatkenheuer, G., Pozniak, A. L., Johnson, M. A., Plettenberg, A., Staszewski, S., Hoepelman, A. I., & Saag, M. S. 563 Goebel FD, Rockstroh JK, Dezube BJ, Jenkins TM, Medhurst C, Sullivan JF, Ridgway C, Abel S, 564 James IT, Youle M, van der Ryst E. 2005. Efficacy of short-term monotherapy with maraviroc, a 565 new CCR5 antagonist, in patients infected with HIV-1. *Nat Med*, *11*, 1170-1172.

Fauci, A. S. 2007. Pathogenesis of HIV disease: opportunities for new prevention interventions. *Clinical Infectious Diseases*, *45*(Supplement_4), S206-S212.

Gadpayle, A. K., Kumar, N., Duggal, A., Rewari, B. B., & Ravi, V. 2012. Survival trend and prognostic outcome of AIDS patients according to age, sex, stages, and mode of transmission–A retrospective study at ART centre of a tertiary care hospital. *Journal, Indian Academy of Clinical Medicine*, *13*(4).

Gali, Y., Berkhout, B., Vanham, G., Bakker, M., Back, N. K., & Ariën, K. K. 2007. Survey of the temporal changes in HIV-1 replicative fitness in the Amsterdam Cohort. *Virology*, *364*(1), 140-146.

Gao, X., Wu, Y., Zhang, Y., Zhang, N., Tang, J., Qiu, J., ... & Du, Y. 2012. Effectiveness of school-based education on HIV/AIDS knowledge, attitude, and behavior among secondary school students in Wuhan, China. *PLoS one*, *7*(9), e44881.

Guerra, J. L. P. 2014. HIV-1 Replicative Capacity Predicts Disease Progression and is Associated with Early Pathogenesis (Doctoral dissertation, Emory University).

Gupta, V., & Gupta, S. 2004. Laboratory markers associated with progression of HIV infection. *Indian journal of medical microbiology*, *22*(1), 7.

Herbeck, J. T., Müller, V., Maust, B. S., Ledergerber, B., Torti, C., Di Giambenedetto, S., ... & Gottlieb, G. S. 2012. Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission. *AIDS (London, England)*, *26*(2), 193.

Hernandez-Vargas, E. A., & Middleton, R. H. 2013. Modeling the three stages in HIV infection. *Journal of theoretical biology*, *320*, 33-40.

Highleyman, L. 2010. Inflammation, immune activation, and HIV. *BETA: bulletin of experimental treatments for AIDS: a publication of the San Francisco AIDS Foundation*, *22*(2), 12-26.

Ho, S. H., Shek, L., Gettie, A., Blanchard, J., & Cheng-Mayer, C. 2005. V3 loop-determined coreceptor preference dictates the dynamics of CD4+-T-cell loss in simian-human immunodeficiency virus-infected macaques. *Journal of virology*, *79*(19), 12296-12303.

Huang, K. H. G., Goedhals, D., Carlson, J. M., Brockman, M. A., Mishra, S., Brumme, Z. L., ... & Heckerman, D. 2011. Progression to AIDS in South Africa is associated with both reverting and compensatory viral mutations. *PloS one*, *6*(4), e19018.

Hunt, P. W., Brenchley, J., Sinclair, E., McCune, J. M., Roland, M., Shafer, K. P., ... & Douek, D. 2008. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *The Journal of infectious diseases*, *197*(1), 126-133.

Ioannidis, J. P., Contopoulos-Ioannidis, D. G., Rosenberg, P. S., Goedert, J. J., De Rossi, A., Espanol, T., ... & Rousseau, C. 2003. Effects of CCR5-Δ32 and CCR2-64I alleles on disease progression of perinatally HIV-1-infected children: an international meta-analysis. *Aids*, *17*(11), 1631-1638.

Ioannidis, J. P., Rosenberg, P. S., Goedert, J. J., Ashton, L. J., Benfield, T. L., Buchbinder, S. P., ... & Kostrikis, L. G. 2001. Effects of CCR5-Δ 32, CCR2-64I, and SDF-1 3′ A alleles on HIV-1 disease progression: an international meta-analysis of individual-patient data. *Annals of internal medicine*, *135*(9), 782-795.

Jiang, H., Xie, N., Cao, B., Tan, L., Fan, Y., Zhang, F., ... & Nie, S. 2013. Determinants of progression to AIDS and death following HIV diagnosis: a retrospective cohort study in Wuhan, China. *PloS one*, *8*(12), e83078.

Jiao Y, Zhang T, Wang R, et al. Plasma IP-10 is associated with rapid disease progression in early HIV-1 infection. Viral Immunol 2012; 25:333–337.

Kanekar, A. 2010. Biomarkers predicting progression of human immunodeficiency virus-related disease. *Journal of clinical medicine research*, *2*(2), 55.

Kiepiela, P., Smith, A. N., & Rosenberg, E. 2005. Laboratory markers associated with progression of HIV infection. *Best Practice & Research Clinical Obstetrics and Gynaecology* Vol. 19, No. 2, pp. 243–254,

Klatt, E. C. 2016. Pathology of HIV/AIDS. *Atherosclerosis". Utah. Edu*.

Klatt, E. C. 2018. Pathology of HIV/AIDS. *Atherosclerosis". Utah. Edu*.

Klimas, N., Koneru, A. O. B., & Fletcher, M. A. 2008. Overview of HIV. *Psychosomatic medicine*, *70*(5), 523-530.

Koethe, J. R., Jenkins, C. A., Shepherd, B. E., Stinnette, S. E., & Sterling, T. R. 2011. An optimal body mass index range associated with improved immune reconstitution among HIV-infected adults initiating antiretroviral therapy. *Clinical infectious diseases*, *53*(9), 952-960.

Koning, F. A., van Rij, R. P., & Schuitemaker, H. (2002). Biological and molecular aspects of HIV-1 coreceptor usage. *infection*, *51*, 64.

Kwantwi, L. B. 2017. *Neopterin as a surrogate marker for monitoring HIV disease progression and patient's response to antiretroviral therapy: a case control study in Kumasi, Ghana* (Doctoral dissertation).

Kwantwi, L. B., Tunu, B. K., Boateng, D., & Quansah, D. Y. 2017. Body Mass Index, Haemoglobin, and Total Lymphocyte Count as a Surrogate for CD4 Count in Resource Limited Settings. *Journal of biomarkers*, *2017*.

Lama, J., & Planelles, V. 2007. Host factors influencing susceptibility to HIV infection and AIDS progression. *Retrovirology*, *4*(1), 52.

Langford, S. E., Ananworanich, J., & Cooper, D. A. 2007. Predictors of disease progression in HIV infection: a review. *AIDS research and therapy*, *4*(1), 11.

Leserman, J. 2008. Role of depression, stress, and trauma in HIV disease progression. *Psychosomatic medicine*, *70*(5), 539-545.

Leserman, J., Petitto, J. M., Golden, R. N., Gaynes, B. N., Gu, H., Perkins, D. O., ... & Evans, D. L. 2000. Impact of stressful life events, depression, social support, coping, and cortisol on progression to AIDS. *American Journal of Psychiatry*, *157*(8), 1221-1228.

Lewden, C., Thiébaut, R., Boufassa, F., Coulibaly, A., Malateste, K., Seng, R., ... & Anglaret, X. 2010. Comparison of early CD4 T-cell count in HIV-1 seroconverters in Cote d'Ivoire and France: the ANRS PRIMO-CI and SEROCO cohorts. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *53*(2), 260-265.

Lovvorn, A. E., Patnaik, P., Walker, C. J., Kwok, C., Van Der Pol, B., Chipato, T., ... & Morrison, C. S. 2010. Variations in CD4 cell counts among HIV-uninfected and infected women in Uganda and Zimbabwe. *International journal of STD & AIDS*, *21*(5), 342-345.

Luckheeram, R. V., Zhou, R., Verma, A. D., & Xia, B. 2012. CD4. *Clinical and developmental immunology*, *2012*.

Mackelprang, R. D., Carrington, M., Thomas, K. K., Hughes, J. P., Baeten, J. M., Wald, A., ... & Gao, X. 2015. Host genetic and viral determinants of HIV-1 RNA set point among HIV-1 seroconverters from sub-saharan Africa. *Journal of virology*, *89*(4), 2104-2111.

Mangili, A., Murman, D. H., Zampini, A. M., Wanke, C. A., & Mayer, K. H. 2006. Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. *Clinical Infectious Diseases*, *42*(6), 836-842.

Martin, M. P., Lederman, M. M., Hutcheson, H. B., Goedert, J. J., Nelson, G. W., Van Kooyk, Y., ... & O'Brien, S. J. 2004. Association of DC-SIGN promoter polymorphism with increased risk for parenteral, but not mucosal, acquisition of

human immunodeficiency virus type 1 infection. *Journal of virology*, *78*(24), 14053-14056.

McMichael, A. J. 2006. HIV vaccines. *Annu. Rev. Immunol.*, *24*, 227-255.

Meyer, L., Chaix, M. L., & Nagy, Z. 2007, July. Low CD4 T cell counts in sub-Saharan African subjects enrolled at the time of HIV-1 primary infection in the French ANRS PRIMO cohort. In *Proceedings of the 4th IAS conference on HIV pathogenis, treatment and prevention*.

Minidis, N. M., Mesner, O., Agan, B. K., & Okulicz, J. F. 2014. Delayed-type hypersensitivity (DTH) test anergy does not impact CD4 reconstitution or normalization of DTH responses during antiretroviral therapy. *Journal of the International AIDS Society*, *17*(1), 18799.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*, *151*(4), 264-269.

Monge, S., Jarrín, I., Pérez-Hoyos, S., Ferreros, I., García-Olalla, P., Muga, R., ... & Del Amo, J. 2011. Educational level and HIV disease progression before and after the introduction of HAART: a cohort study in 989 HIV seroconverters in Spain. *Sex Transm Infect*, sextrans-2011.

Moreno, J. 2014. Viral and host factors involved in rapid HIV-1 disease progression. Institut de Recerca de la Sida IrsiCaixa Doctoral Thesis

Mothe, B., Ibarrondo, J., Llano, A., & Brander, C. 2009 Virological, immune and host genetics markers in the control of HIV infection. *Disease markers*, *27*(3-4), 105-120.

Müller, V., Fraser, C., & Herbeck, J. T. 2011. A strong case for viral genetic factors in HIV virulence. *Viruses*, *3*(3), 204-216.

Murray, M. D., D.G. Morrow, M. Weiner, D.O. Clark, W.Tu, M.M. Deer, D.C. Brater and M. Weinberger 2004. A conceptual framework to study medication adherence in older adults. *The American Journal of Geriatric Pharmacotherapy, 2*: 36-43.

Mussini, C., Lorenzini, P., Cozzi-Lepri, A., Lapadula, G., Marchetti, G., Nicastri, E., ... & Monforte, A. D. A. 2015. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. *The lancet HIV*, *2*(3), e98-e106.

Nyamweya, S., Hegedus, A., Jaye, A., Rowland-Jones, S., Flanagan, K. L., & Macallan, D. C. 2013. Comparing HIV-1 and HIV-2 infection: Lessons for viral immunopathogenesis. *Reviews in medical virology*, *23*(4), 221-240.

O'Connell, K. A., Bailey, J. R., & Blankson, J. N. 2009. Elucidating the elite: mechanisms of control in HIV-1 infection. *Trends in pharmacological sciences*, *30*(12), 631-637.

Obirikorang, C., & Yeboah, F. A. 2009. Blood haemoglobin measurement as a predictive indicator for the progression of HIV/AIDS in resource-limited setting. *Journal of biomedical science*, *16*(1), 102.

Onyango-Ochieng, W. 2009.*Cultural practices in sexuality and reproductive health among the Luo in Kenya*. Unpl. MA thesis submitted to the Institute of Cultural Studies, The University of Amsterdam.

Pantazis, N., Morrison, C., Amornkul, P. N., Lewden, C., Salata, R. A., Minga, A., ... & Porter, K. 2012. Differences in HIV natural history among African and non-African seroconverters in Europe and seroconverters in sub-Saharan Africa. *PloS one*, *7*(3), e32369.

Parker, R. and Aggleton, P. 2003. HIV and AIDS-related stigma and discrimination: A conceptual framework and implications for action. *Social Science and Medicine*, 57:13-24

Perno, C. F., Moyle, G., Tsoukas, C., Ratanasuwan, W., Gatell, J., & Schechter, M. 2008. Overcoming resistance to existing therapies in HIV-infected patients: The role of new antiretroviral drugs. *Journal of medical virology*, *80*(4), 565-576.

Polis, M. A., & Masur, H. 1990. Predicting the progression to AIDS. *The American journal of medicine*, *89*(6), 701-705.

Pontali, E., B. Vareldzis, J. Perrien and J.P. Narain 2003. Antiretroviral treatment in resource limited settings. *Journal of Health Management,* 5:315-326

Prince, J. L., Claiborne, D. T., Carlson, J. M., Schaefer, M., Yu, T., Lahki, S., ... & Goepfert, P. 2012. Role of transmitted Gag CTL polymorphisms in defining replicative capacity and early HIV-1 pathogenesis. *PLoS pathogens*, *8*(11), e1003041.

Prince, J. L., Claiborne, D. T., Carlson, J. M., Schaefer, M., Yu, T., Lahki, S., ... & Goepfert, P. 2012. Role of transmitted Gag CTL polymorphisms in defining replicative capacity and early HIV-1 pathogenesis. *PLoS pathogens*, *8*(11), e1003041.

Rachlis, B. S., Mills, E. J., & Cole, D. C. 2011. Livelihood security and adherence to antiretroviral therapy in low and middle income settings: a systematic review. *PloS one*, *6*(5), e18948.

Richman, D.D., et al. 2003. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc Natl Acad Sci U S A, 100(7): 4144-9.

Sauce, D., Larsen, M., Fastenackels, S., Pauchard, M., Ait-Mohand, H., Schneider, L., ... & Bailey, M. 2011. HIV disease progression despite suppression of viral replication is associated with exhaustion of lymphopoiesis. *Blood*, blood-2011.

Schuerwegh, A. J., Dombrecht, E. J., Stevens, W. J., Van Offel, J. F., Bridts, C. H., & De Clerck, L. S. 2003. Influence of pro-inflammatory (IL-1α, IL-6, TNF-α, IFN-γ) and anti-inflammatory (IL-4) cytokines on chondrocyte function. *Osteoarthritis and cartilage*, *11*(9), 681-687.

Schweitzer, A. M., Mizwa, M. B., & Ross, M. W. 2010. Psychosocial aspects of HIV/AIDS adults. *Baylor Int Ped AIDS Initiative*, 334-49.

Shah, S., Smith, C. J., Lampe, F., Youle, M., Johnson, M. A., Phillips, A. N., & Sabin, C. A. 2007. Haemoglobin and albumin as markers of HIV disease progression in the highly active antiretrovial therapy era: relationships with gender. *HIV medicine*, *8*(1), 38-45.

Silva, M. D. O., Bastos, M., Martins Netto, E., Gouvea, N. A. D. L., Torres, A. J. L., Kallas, E., ... & Brites, C. 2010. Acute HIV infection with rapid progression to AIDS. *Brazilian Journal of Infectious Diseases*, *14*(3), 291-293.

Ssemwanga, D., Nsubuga, R. N., Mayanja, B. N., Lyagoba, F., Magambo, B., Yirrell, D., ... & Kaleebu, P. 2013. Effect of HIV-1 subtypes on disease progression in rural Uganda: a prospective clinical cohort study. *PloS one*, *8*(8), e71768.

Stebbing, J., Gazzard, B., & Douek, D. C. 2004. Where does HIV live?. *New England Journal of Medicine*, *350*(18), 1872-1880

ten Ham-Baloyi, W., & Jordan, P. 2016. Systematic review as a research method in postgraduate nursing education. *health sa gesondheid*, *21*(1), 120-128.

Torres, R. A., & Lewis, W. 2014. Aging and HIV/AIDS: pathogenetic role of therapeutic side effects. *Laboratory investigation*, *94*(2), 120.

Tsoukas, C. M., & Bernard, N. F. 1994. Markers predicting progression of human immunodeficiency virus-related disease. *Clinical Microbiology Reviews*, *7*(1), 14-28.

Turk, G., Ghiglione, Y., Hormanstorfer, M., Laufer, N., Coloccini, R., Salido, J., ... & Caruso, M. P. 2018. Biomarkers of Progression after HIV Acute/Early Infection: Nothing Compares to CD4+ T-cell Count?. *Viruses*, *10*(1), 34.

University of York. Centre for Reviews and Dissemination. 2009. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. University of York, Centre for Reviews & Dissemination.

van Montfort, T., Nabatov, A. A., Geijtenbeek, T. B., Pollakis, G., & Paxton, W. A. 2007. Efficient capture of antibody neutralized HIV-1 by cells expressing DC-SIGN and transfer to CD4+ T lymphocytes. *The Journal of Immunology*, *178*(5), 3177-3185.

van Montfort, T., Thomas, A. A., Pollakis, G., & Paxton, W. A. 2008. Dendritic cells preferentially transfer CXCR4-using human immunodeficiency virus type 1 variants to CD4+ T lymphocytes in trans. *Journal of virology*, *82*(16), 7886-7896.

Venkataramana, K. 2013. A study of biological markers in HIV disease progression and management in the highly active antiretroviral therapy (HAART) era. *American Journal of Bioscience and bioengineering*, *1*(2), 24-37.

WHO: scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. Edited by: Hammer S. Geneva , World Health Organisation 3 by 5 Initiative; 2004:1-68.

Wong, S. S. L., Wilczynski, N. L., & Haynes, R. B. 2006. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. *Journal of the Medical Library Association*, *94*(4), 451.

Wood, E., Hogg, R. S., Lima, V. D., Kerr, T., Yip, B., Marshall, B. D., & Montaner, J. S. 2008. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. *Jama*, *300*(5), 550-554.

Wright, J. K., Novitsky, V., Brockman, M. A., Brumme, Z. L., Brumme, C. J., Carlson, J. M., ... & van der Stok, M. 2011. Influence of Gag-protease-mediated replication capacity on disease progression in individuals recently infected with HIV-1 subtype C. *Journal of virology*, *85*(8), 3996-4006.

Yue, L., Prentice, H. A., Farmer, P., Song, W., He, D., Lakhi, S., ... & Kaslow, R. A. 2012. Cumulative impact of host and viral factors on HIV-1 viral load control during early infection. *Journal of virology*, JVI-02118.