HAEMATOLOGICAL AND IMMUNOLOGICAL ABNORMALITIES IN HIV INFECTED ADULT PATIENTS AT THIKA LEVEL FIVE HOSPITAL COMPREHENSIVE CARE CENTRE, KIAMBU COUNTY, KENYA

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DECLARATION AND APPROVAL

Declaration by the Student

I declare that this research thesis is my original work and has not been presented for the academic award of a degree in any university or any other institution.

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DEDICATION

This research thesis is dedicated to my entire family and close friends.

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ABSTRACT

Human Immunodeficiency Virus (HIV) remains a global issue that causes considerable morbidity and mortality, particularly in sub-Saharan Africa, where greater than 70% of all HIV patients exist. HIV is a multisystem disease and haematological and immunological abnormalities have been reported as among the most frequent complications of HIV infection. CD4+ T cell loss, dysregulation of the cytokine profile and immune system dysfunction are among the immunological changes. Haematological abnormalities involve the three major cell lineages leading to impaired haematopoiesis and cytopenias. This study purpose was to investigate the haematological and immunological abnormalities in HIV infected adult patients at Thika Level Five Hospital CCC, in Kiambu County, Kenya. This cross sectional case control study enrolled 237 subjects who included HIV positive ART- naïve, HIV- positive ART- treated and HIV-negative controls. Sociodemographic information and clinical history data was gathered using a pretested structured questionnaire and from health records. Blood samples were collected and analysed for haematological and immunological (CD4) parameters. Student's t-tests were employed to compare demographic and laboratory characteristics between groups. Fisher's exact test was used to determine relationship between immunohaematological abnormalities and ART regimen. A P-value of <0.05 was considered statistically significant. Anaemia, leucopenia and thrombocytopenia were common haematological abnormalities in both ART – treated and ART – naïve HIV infected patients. Overall, leucopenia was the most common haematological abnormality followed by anemia and thrombocytopenia with an overall frequency of 18.9%, 15.2% and 2.5% respectively. The mean ± SD of PLT, ALC, HB, MCV, MCH, PCV, of ART – treated was significantly higher compared with mean ± SD of ART – naïve; 410.80±217.10 vs 309.30±147.90 (p =0.0030), 2.03±0.66 vs 1.50±0.66 (p <0.0001), 13.96± 2.01 vs 12.63±2.99 (p =0.0054), 90.35±10.48 vs 82.92±9.42 (p <0.0001), 27.76±3.18 vs 25.83±3.50 (p =0.0013), 45.53±6.29 vs 40.57±9.13 (p =0.0008) respectively. The mean ± SD CD4 count (378.50±317.7) of ART – treated was higher compared to mean (348.50±256.90) of ART – naïve but not significantly different (p =0.5045). The ART regimen significantly influenced ALC, PCV, MCV, MCH, RDW and CD4 count abnormalities (p- value < 0.05). Patients on TDF/3TC/DTG had significantly higher cases of lymphopenia (P = 0.0252). Macrocytosis was significantly higher in those on AZT/3TC/ATV/r (p- value <0.0001). Low HB (p-value = 0.0021) and low MCH (p-value = 0.0050) were significantly higher in females compared to males. Patient age significantly influenced the PLT abnormality (p-value = 0.003). ART duration significantly influenced WBC abnormality (p-value = 0.0125) and ALC abnormality (p-value <0.0001) of the study subjects. Low CD4 count was associated with thrombocytopenia (p value = 0.0012). Covid -19 vaccine type significantly influenced PLT (p value = 0.0401) and ANC abnormality (p value = 0.0010). HIV infected patients ought to be routinely monitored for haematological and immunological abnormalities followed by appropriate therapeutic interventions so as to improve their quality of life and reduce morbidity and mortality. Haematological parameters can be used as a screening test to assess the severity of HIV infection and response to ART. Optimizing ART regimens to minimize haematological complications is essential for reducing the burden of HIV-related complications.

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LIST OF ABBBREVIATIONS AND ACRONYMS

ADRs	Adverse Drug Reactions
AIDS	Acquired Immunodeficiency Syndrome
ANC	Absolute Neutrophil Count
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Azidothymidine
cART	Combination Antiretroviral Therapy
CBC	Complete Blood Count
CCC	Comprehensive Care Clinic
CD4	Cluster of Differentiation 4
CFU –E	Colony Forming Units – Erythroid
HAART	Highly Active Antiretroviral Therapy
HCT	Hematocrit
Hgb	Hemoglobin
HGFs	Haemopoietic Growth Factors
HIV	Human Immunodeficiency Virus
IL	Interleukins
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
PLT	Platelets
PLWHA	People Living With HIV/AIDS

RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SSA	Sub Saharan Africa
TLC	Total Leukocyte Count
UNAIDS	United Nations Programme on HIV/AIDS
VL	Viral Load
WBC	White Blood Cells
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 Background Information

The human immunodeficiency virus (HIV) pandemic is currently one of the most pressing health dangers the world has ever faced. About 78 million people have been infected with HIV since the epidemic began and 35 million deaths have occurred due to AIDS – related ailments (UNAIDS, 2016). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) global estimates, there were 38.0 million people living with HIV by the end of 2019. In the same year approximately 1.7 million people were newly infected and around 690 000 people died from AIDS-related ailments globally (UNAIDS 2020).

The global burden of HIV/AIDS remains highest in Sub –Saharan Africa with greater than 2/3 of all PLHIV worldwide (UNAIDS). Almost every country in sub-Saharan Africa has a widespread HIV epidemic, that is to say, more than 1% of the populace is infected. South Africa has the highest number of people living with HIV in the world (7.5 million). The highest world's HIV prevalence (27%) is found in Eswatini (previously named Swaziland (UNAIDS). About 54% of the PLHIV are found in Eastern and Southern Africa and in 2018 approximately 800 000 people were newly infected and 310, 000 AIDS –affiliated deaths were recorded in eastern and southern Africa (UNAIDS 2019). Additionally, 730,000- new infections and 300, 000 deaths due to AIDS occurred in the same region (UNAIDS, 2020). As per the 2019 UNAIDS special analysis, eastern and southern African region's had an estimated 20.6 million PLHIV and the percentage of individuals who were aware of their HIV status rose from 77% in 2015 to 85% in 2018. Approximately 67% of PLHIV were on ART, an increase of 14% (up from 53%) in 2015), while

58% had undetectable levels of HIV virus (viral suppression), an increase of 15% (up from 43%) from the year 2015) (UNAIDS, 2019).

In 2018, Kenya, together with Tanzania, had the third-largest HIV epidemic globally with roughly 1.6 million PLHIV (UNAIDS AIDS info,). About 25,000 deaths from AIDS-associated illnesses occurred in 2018. While this fatality rate is still high, it has progressively declined from 64,000 in 2010 (UNAIDS AIDS info). In 2015, Kenya adopted the World Health Organization's recommendations to immediately offer treatment to people diagnosed with HIV (UNAIDS 2017). Consequently, antiretroviral treatment (ART) was accessible to about 940,000 adults and 60,000 children in 2016. This amounts to 64% of adults and 65% of children who need ART being able to receive it (UNAIDS, 2017). The 2017 National HIV prevalence rate among adults was approximated at 4.9% with women having a higher prevalence (5.2%) than men (4.5%). The HIV epidemic in Kenya is diversified from one geographical region to another, with prevalence rates spanning from a prevalence of 21.0% in Siaya County to approximately 0.1% in Wajir County while the 2017 Kiambu HIV prevalence rate was 4.0% (NASCOP, 2018). In addition, the number of yearly new HIV infections in adults aged 15 and above decreased by 30% from 63,700 in 2010 to 44,800 in 2017. This could be attributed to the expansion of diverse preventive and treatment programmes. As per the report of 2018 Kenya HIV estimates, the ART coverage was approximated to be 75% and 82% in adults and children respectively in 2017. It is approximated that by the end of 2017, 635,500 lives in Kenya had been saved by the expansion of ART since 2004 by preventing AIDS-associated deaths (NASCOP, 2018).

It has been established that infection with HIV linked with diverse immunological and haematological changes. CD4+ T cell loss, dysregulation of the cytokine profile and immune dysfunction are among the immunological changes. The most prominent immunologic characteristic of HIV infection is increasing CD4+ T cell loss, consequently resulting to immunodeficiency (Wan et al., 2015). HIV infected individuals frequently manifest with haematological abnormalities especially the pancytopenias as a result of disrupted haematopoiesis and a compromised immune system. The causes of these haematological abnormalities is compounded and many factors which include decreased haematopoiesis due to drug effects, myelosuppression due to infiltration of infectious agents or neoplasms, impaired haematopoiesis due to HIV infection itself, among others (Durandt et al., 2019). Since hematological issues in individuals with HIV are frequent and involve multiple factors, a comprehensive and methodical approach is crucial, taking into account possible contributing factors like medications and BM infiltration from opportunistic infections and/or cancers (Opie, 2024). The pysiopathology of these haematological abnormalities are not yet fully expounded, but it is thought to be complex and multifaceted (Vishnu and Aboulafia, 2015). The most frequently observed hematologic abnormalities (outcomes) in HIV/AIDS patients include the cytopenias, that is, anemia, thrombocytopenia, leucopenia, lymphopenia, neutropenia, and thrombocytopenia (Ashenafi et al., 2023). Cytopenias may affect any of the major blood cell lines leading to lowered red blood cells, white blood cell and platelets counts (Vishnu and Aboulafia, 2015; Opie, 2012). It is thought that these are caused directly by effects of HIV infection, secondary infections or ARV drugs adverse effects (Camara-Lemarroy, 2015).

Anaemia has been reported to be the most common haematological abnormality in HIV infected patients and its severity increases as the CD4 count decreases (Usman et al., 2023). The causes of anemia among HIV-infected patients are multifactorial which include the direct and indirect impact on the survival and functioning of bone marrow hematopoietic stem/progenitor cells (HSPCs) (Marchionatti & Parisi, 2021; Durandt et al., 2019). In addition, the drugs used for ART, inflammatory mediators released during HIV infection and coinfections or opportunistic infections could also affect the proliferation and differentiation of HSPCs during hematopoiesis (Marchionatti & Parisi, 2021; Durandt et al., 2019).

Leucopenia has been shown to be the common hematological abnormality found in individuals with HIV infection in some studies. The factors contributing to HIV-related leucopenia are diverse, including the direct impact of HIV, autoimmune conditions, neoplasms, ART drugs (particularly zidovudine-based regimens), cotrimoxazole, and opportunistic infections (Gebreweld et al., 2020; Fekene et al., 2018; Afari and Blay, 2018). The prevalence of leucopenia of HIV-infected adults on ART in sub-Saharan Africa, has been reported to range between 13.4% and 24.4% and HIV patients with low CD4+ cell count to have a higher odds of leucopenia than those with higher CD4+ cell count at the time of antiretroviral-treatment initiation. (Tamir et al., 2019; Kyeyune et al., 2014; Gunda et al., 2017; Fekene et al., 2018; Tarlagia et al., 2021). Most studies indicate that the prevalence of leucopenia is greater in untreated individuals compared to those who have received treatment (Fekene et al., 2018; Afari and Blay, 2018; Tamir et al., 2019).

Thrombocytopenia is a common complication that may arise during any phase of HIV infection (Tamir et al., 2019). Thrombocytopenia ranks as the second most frequent complication after anemia, occurring in 3–40% of people with HIV infection (Enawgaw et al., 2014). The potential mechanisms leading to thrombocytopenia involve immune-mediated destruction of platelets, malfunctioning megakaryocytes, a direct assault on megakaryocytes by the HIV virus, hypersplenism, opportunistic infections, cancer, and the myelosuppressive effects of medications (Gebreweld et al., 2020; Khayati et al., 2020). The estimated prevalence of thrombocytopenia in individuals with HIV/AIDS is between 4.1% and 26.7% (Durandit et al., 2019). A high prevalence of thrombocytopenia and leucopenia has ben reported among people living with HIV/AIDS (Bisetegn & Ebrahim, 2021).

The key treatment goals of ART are to minimize morbidity and mortality associated with HIV, enhance the quality of life, restore and sustain the body's immunological function, and bring about a long-lasting suppression of the viral load (Hoffman et al., 2008).

The advent of highly active antiretroviral therapy (ART) and its widespread use have dramatically altered the natural history of HIV/AIDS. In reality, enhancement in the quality of life, the survival and prognosis of people living with HIV/AIDS (PLWHA) have significantly improved over time. For example, AIDS-related deaths between 2005 and 2015 have decreased by 45 percent (UNAIDS, 2016). Even so, ART use has been linked with grave adverse drug reactions (ADRs) which have resulted in modification of ART regimen in HIV-infected people in sub-Saharan Africa (Jaquet et al., 2011; Brainstein et al., 2010). ADRs may lead HIV patients discontinuing ART, which then causes treatment failure, switching or altering ART regimens, and thus promote greater HIV drug resistance and poorer health (Shet et al., 2014). In addition, owing to increased prevalence of concomitant conditions, overburdened health services and financial limitations that would hinder close monitoring and review of patients on HAART, the incidence of ADRs may be greater in economically developing nations (Subbaraman et al., 2007; KPMG 2012; Kaseje D, 2006). The burden of both toxic and metabolic ART-related complications can be predicted to grow in the coming years, particularly in SSA, which is the world’s nerve center of the HIV pandemic (Nansseu and Bigna, 2017). There is little awareness of ARV drugs toxicity in developing countries (WHO 2007) unlike in developed countries, where the incidents and magnitude of ADRs are well established (Wangai et al., 2011). It is therefore necessary to generate local data that can be used to inform recommendations for the use and choice of ART and improve the ART programme in the country.

Infection with HIV is linked with haematological abnormalities such as anaemia and pancytopenias (Parinitha and Kulkarni, 2012; Durandt et al., 2019) and that haematologic toxicity is one of the adverse drug reactions resulting from treatment with ART. For instance, zidovudine and dideoxycytidine hinder erythroid colony forming units (CFU-E) necessary for erythroid formation and granulocyte macrophage colony forming units that are essential for formation of granulocytes (Balakrishnan et al., 2010). Adversa Drug Reactions (ADRs) include liver toxicity (Kovari et al 2016; Nuñez et al.,2006), haematological abnormalities (Enawgaw et al., 2014), bone marrow suppression, anaemia and neutropenia (Ikunaiye et al., 2018; NASCOP, 2018; NASCOP, 2016; WHO, 2006). This study seeks to evaluate the haematological pand immunological abnormalities in a cohort of HIV infected adult patients at Thika level 5 Hospital Comprehensive Care Centre, Kiambu County, Kenya.

1.2 Statement of the Problem

Human Immunodeficiency Virus (HIV) remains a global issue that causes considerable morbidity and mortality all over the world, particularly in sub-Saharan Africa, where greater than 70% of all HIV patients exist. (WHO, 2015). It has been established that infection with HIV is linked with diverse immunological and haematological changes. CD4+ T cell loss, dysregulation of the cytokine profile and immune dysfunction are among the immunological changes. The most prominent immunologic characteristic of HIV infection is increasing CD4+ T cell loss which leads to reversal of the normal CD4:CD8 ratio consequently resulting to immunodeficiency. Infection and diminishing of CD4+ T cells could produce severe immunodeficiency in HIV infected patients (Wan Majdiah et al., 2015). CD4+ cell levels which corresponds with HIV infection severity, presence of opportunistic infections is used to assess the patient's immunological status and serves as a key guidance as to when HAART should be initiated as well as the timing when prophylactic treatment for opportunistic infections should commence or stop. (Mocroft et al., 2013; Sulliva et al., 1998). CD4 cell count and VL are still the two most reliable predictors and surrogate markers of HIV disease progression frequently used to monitor the infection, managing of HIV/AIDS patients as well as forecasting HIV progression and/or treatment results (Maartens et al., 2014; Hofman et al., 2010). Continued loss of CD4+ T-cells is linked to advancement of HIV disease as well as a higher probability of opportunistic infections and other HIV related clinical events such as body wasting and death. Generally, as HIV disease progresses, the percent of CD4+ cells or CD4+ absolute numbers gradually decline (Ratman et al., 2018).

Haematological abnormalities are typical complicacies of HIV infection and they escalate as the disease progresses. These haematological abberrations are linked to higher morbidity and death rate in HIV positive patients thus negatively impacting their quality of life (Abebe and Alemseged 2009). Haematological presentations are diversified in nature and may cause life-threatening symptoms, reduce the patient's quality of life as well as impede therapy towards primary HIV infection, opportunistic diseases or HIV-related neoplastic disease (Kathuria et al., 2016; Attiliv et al 2008;). Cytopenias (Anemia, leucopenia and thrombocytopenia) may be due to the direct effects of HIV infection, secondary infections or side effects of anti-retroviral therapy (Camara-Lemarroy et al., 2015). Cytokines and growth factors mediated body responses also results in decreased hematopoiesis, antibody- mediated cytopenias and other abnormalities, affecting all the major blood cells lines (Servais et al., 2001). The aetiology of these haematological changes and the mechanisms leading to these changes in HIV infected patients on ART are not fully understood.

Effective HAART subdues the replication of the virus at various stages of HIV life cycle, ameliorates the immune status of the patient and slows down ART drugs resistance. Generally, HAART improves HIV disease prognosis significantly (Hileman and Funderburg 2017). However, combination ART (cART) has been associated with serious and life threatening adverse effects that have been identified as a key safety issue that is reducing the clinical benefits of these medications (Eluwa et al., 2012). Especially, hepatic toxicity (Kovari et al., 2016; Nuñez et al., 2006) and haematological abnormalities (Enawgaw et al., 2014) are frequent negatively impacting the quality of life in addition to being linked to advancement of HIV/AIDS and reduced patient survival. In spite of this, Laboratory evidenced data on the haematological and immunological abnormalities of both ART- treated and ART-naïve HIV infected adult patients at Thika Level Five Hospital Comprehensive Care Centre, in Kiambu County, Kenya, has not been documented. Such data that would guide clinicians in the choice of ART regimens and management of HIV infected patients at thika level five hospital Comprehensive Care Centre is lacking.

With unparalleled number of individuals starting ART in sub-Saharan Africa, the tracking of ART-associated toxicity must be accustomed to guide recommendations for ART use. In fact, as a result of absence of pharmacovigilance systems in low and middle-income countries long-term safety information of ART is still inadequate. Nonetheless, in sub-Saharan Africa, ART-related side effects are frequent and are the leading cause of treatment adjustment in HIV-positive patients receiving ART (Jaquet et al., 2011; Braitstein et al., 2010). Inspite of the benefits of antiretroviral therapy, use of ART could have a positive or negative effect on the levels of these haematological and immunological parameters. The levels of these haematological and immunological parameters, these parameters abnormalities and their associated factors and the comparison studies between the ART -naïve and ART- treated HIV positive patients at Thika Level Five Hospital CCC in Kiambu County are lacking. Therefore, this study purpose was to determine the haematological and immunological abnormalities and the associated factors of HIV infected adult patients at TL5H CCC, Kiambu County, Kenya.

1.3 Justification of the study

Monitoring the HIV – positive patients' haematological and immunological profile for potential detection of the development of hematological and immunological abnormalities will help to plan patient treatment and management and improve treatment outcomes. Understanding changes in the levels of haematological and immunological parameters in HIV- positive patients on ART will guide in the choices of ART regimens and development of novel interventions to mitigate adverse outcomes. Data on levels of haematological and immunological parameters of HIV- infected ART-naïve and ART- treated patients in Kiambu county is not yet documented.

Understanding the effect of ART in the pathogenesis of HIV-associated haematological abnormalities, is key in devising future therapy targets, patient treatment and management strategies that will help in reducing HIV related mortality and morbidity. Currently, comparative data on haematological and immunological abnormalities between ART-naive and ART-exposed individuals and the associated factors remain scarce in Kenya. Data emanating from this study will provide important laboratory based information that will guide in the choice of ART regimens that poses minimal haematological toxicity and negative effects to the HIV- infected patients. This study will also elucidate other markers that can be used in resource limited settings or in developing countries such as Kenya to monitor HIV disease progression other than the viral load which is more expensive.

Thika level five hospital was chosen as the study site because the hospital is located in a cosmopolitan town and TL5H comprehensice care center is a high volume capacity facility that has a high number of HIV- infected patients enrolled at the CCC than the others centres in Kiambu County and it is also well equipped than the other comprehensive care centres. In addition, the hospital serves patients from the neighbouring counties such as muranga, Nairobi and Machakos County

1.4 Objectives

1.4.1 General Objective

To determine the haematological and immunological abnormalities in HIV infected adult patients at Thika Level Five Hospital Comprehensive Care Clinic, Kiambu County, Kenya.

1.4.2 Specific objectives

1. To evaluate the distribution and magnitude of Haematological and Immunological abnormalities in the HIV- infected ART – treated, HIV- infected ART – naïve and controls at TL5H CCC.
2. To Compare the Haematological and Immunological Parameters between the ART – treated and ART – naïve HIV infected patients and controls at TL5H CCC.
3. To determine the influence of ART regimen type on the haematological and immunological abnormalities of HIV infected ART- treated adult patients at TL5H CCC.
4. To determine the relationship between sociodemographic factors and clinical characteristics with haematological abnormalities in HIV infected patients at TL5H CCC

1.5 Research Questions

1. What is the distribution and magnitude of Haematological and Immunological abnormalities in the HIV- infected ART – treated, HIV- infected ART – naïve and controls at TL5H CCC?
2. What is the comparison in the Haematological and Immunological Parameters between the ART – treated and ART – naïve HIV infected patients at TL5H CCC?
3. What is the influence of the ART regimen type on haematological & immunological abnormalities of HIV infected ART- treated adult patients at TL5H CCC?
4. What is the relationship between sociodemographic factors and clinical characteristics with haematological abnormalities in HIV infected patients at TL5H CCC?

1.6 Scope of the study

The focus of this study was the haematological and immunological abnormalities in both ART – naïve and ART – treated HIV –infected adult patients at the Thika Level Five Hospital Comprehensive Care Centre in Kiambu County. The following crucial elements were examined within the scope of this investigation.

The haematological abnormalities included: The specific haematological abnormalities covered were the abnormalities in the levels of the three major blood cells, that is, white blood cells, red blood cells and platelets including the neutrophils, lymphocytes, monocytes, haemoglobin concentration, packed cell volume and the red blood cell indices. The distribution and magnitude of these abnormalities in both ART –naïve and ART – treated was compared.

Immunological abnormalities included: This study covered only the abnormalities in the blood levels of immunological marker CD4. The distribution and magnitude of these abnormalities in both ART –naïve and ART – treated was compared.

The ART regimens: The study focused on only five types of ART regimens that were being used by the HIV - infected patients at the Thika Level Five Hospital CCC. These are AZT/3TC/ATV/r, TDF/3TC/DTG, TDF/3TC/ATV/r, ABC/3TC/ATV/r and AZT/3TC/DTG. The correlation of these ART regimens with the haematological and immunological abnormalities of ART – treated HIV- infected patients was assessed.

The factors associated with haematological abnormalities: The specific factors studied were the sociodemographic factors (gender, age, marital status) and the clinical characteristics (Body Mass Index (BMI), cotrimoxazole use, hepatitis A, B & C co-infection, ART duration, HIV- disease stage based on CD4 count and Covid -19 vaccine type). The study assessed the influence of these factors on the haematological abnormalities of the HIV – infected patients.

1.7 Limitations of the study

Some of the limitations of the current study are unwillingness of some of the HIV infected patients to participate in the study thus the study took long to achieve the desired sample size. Also, this study was not able to identify all the haematological and immunological abnormalities in HIV patients such as the coagulation profile abnormalities and CD8 count due to logistic reasons. The major limitation of this study is its cross-sectional design that was employed in this study which does not allow causal relationships between independent variables and cytopenias to be drawn. Therefore, it is recommended that a large scale longitudinal study covering several HIV comprehensive care centres within Kiambu County and even in different counties of Kenya be done so as to extrapolate the relevant findings from this study

1.8 Delimitations

1. The haematological abnormalities covered were the complete blood cell count abnormalities only and those of the coagulation profile were left out.
2. The immunological abnormalities covered in this study were only those of CD4 count and the other immunological markers were not included in the study.
3. The study covered Thika Level Five Hospital CCC only and left out the other comprehensive care centres in Kiambu County. Thika Level Five Hospital CCC is a high volume capacity facility with a high number of HIV- infected patients enrolled in the CCC than the others centres in Kiambu County and it is also well equipped than the other comprehensive care centres.

1.9 Study assumptions

That the study participants will give honest and factual responses to the interview questions. To achieve honest and accurate information from the study participants they were assured of privacy and confidentiality of the information that they give to the researcher. This was by use of unique codes rather than patient names and restriction of access to the data by unauthorized people. That the time to conduct the study will be adequate. That the required financial and infrastructural resources will be available and sufficient throughout the study period

CHAPTER TWO

LITERATURE REVIEW

2.1 Human Immunodeficiency Virus

2.1.1 Transmission of HIV

Transmission of HIV from person to person occurs primarily via three routes: exposure to genital fluids (i.e., sexual transmission), exposure to blood and blood products (e.g., intravenous drug use or transfusions) and through maternal-to-child transmission (i.e., intrapartum or via breast milk). Although other bodily fluids such as cerebrospinal fluid, synovial fluid, and ascites fluid can harbor virus, transmission from these other fluids is extremely rare and typically only a consideration in healthcare-worker exposures. Non-bloody urine, saliva, feces, and vomitus pose no transmission risk. While transmission has classically been considered to occur when cell-free virus infects susceptible host cells, there is increasing appreciation that cell-associated virus may play an important role in transmission (Romen et al., 2015).

Regardless, the risk of transmission for all of these mechanisms depends on the susceptibility of the recipient to infection and on host factors including the amount of virus in the infectious body fluid. For example, the risk of sexual transmission varies based on the sex act, the presence of concurrent genital ulcerative diseases like herpes simplex virus and syphilis, the source patient viral load, host viral factors, and recipient immune factors (Patel et al., 2014).

The most common route of transmission worldwide is from exposure to genital fluids via sexual intercourse. Unprotected receptive anal intercourse poses the greatest sexual transmission risk—more than 10 times greater than unprotected insertive anal intercourse, while receptive and insertive penile vaginal intercourse transmission risks are lower yet (Patel et al., 2014).

Effective antiretroviral therapy (ART) can dramatically impact transmission risk. Recent data from the HPTN 052 trial clearly demonstrate that transmission between HIV-discordant partners is extremely low when the infected partner has undetectable viremia. This study followed 1,763 discordant, primarily heterosexual couples, and among those on therapy, transmissions linked to the partner on effective therapy, known as combination antiretroviral therapy, occurred in only eight couples. In four cases, the infected partner had only recently been started on therapy, and the remaining four transmissions occurred after loss of virologic control (Eshleman et al., 2015). This study and other observational studies have changed the paradigm of HIV treatment and prevention worldwide, leading to recommendations to treat all HIV-infected persons regardless of CD4 count. Importantly, this trial introduced the concept that treatment is the most effective means of prevention of new infections, but with continued emphasis on the use of condoms, preexposure prophylaxis, and behavioral changes (Ford et al., 2017).

2.1.1 The life cycle of HIV

The human immunodeficiency virus (HIV) goes through a variety of phases throughout an infection, collectively known as its life cycle. The immune system's CD4 cells, also known as CD4 T lymphocytes, are targeted and killed by HIV (Rossi et al., 2021). Among the many white blood cells in the body, CD4 cells are crucial for fighting off infections. In order to replicate and disseminate, HIV makes use of the CD4 cell machinery. The HIV life cycle describes this process, which consists of seven distinct phases.

2.1.2 Binding Stage

The HIV life cycle begins with the binding stage, when the virus finds its host, the immune system's CD4 cells. The first step in this process is for a viral glycoprotein known as gp120 to bind to CD4 receptors on these cells' surface. This protein on the HIV envelope interacts to the CD4 receptor and undergoes a cascade of modifications when it does so. In order to facilitate interactions with co-receptors, such CCR5 or CXCR4, that are located on the surface of CD4 cells, this binding causes conformational changes in gp120, which expose certain areas of the protein (Chen, 2019). These interactions cause gp41, another viral glycoprotein, to undergo further conformational changes, which ultimately result in the creation of a fusion complex. The V3 loop becomes visible when gp120 goes through structural changes upon binding to the CD4 receptor. The V3 loop, which is accessible, helps the CD4 cell connect with a surface-bound co-receptor. Several immune cells include the co-receptors CCR5 and CXCR4, which are used by HIV. Upon binding to the co-receptor, which is usually CCR5 or CXCR4, gp120 and another viral glycoprotein known as gp41 undergo further structural modifications. Because of these changes, a fusion complex is formed when the viral and cellular membranes fuse. The viral envelope and the cell membrane are brought together in this complex, which allows them to fuse. The complicated rearrangements in the viral envelope glycoproteins, especially gp41, cause the membranes to merge, enabling the genetic viral core to enter the CD4 cell's cytoplasm. In the end, the viral core—which contains the HIV genetic material (RNA)—is able to enter the CD4 cell's cytoplasm via a hole created when the viral envelope unites with the cell membrane. During this binding stage, the HIV life cycle begins inside the host cell and is defined by specific interactions between viral proteins and cellular receptors. This contact sets the scene for succeeding stages of the viral life cycle. In order for the HIV virus to infect host cells, it must first reach the binding stage of its life cycle (Rojas and Park, 2019).

The immune system's CD4 cells, which are crucial for defence, are the intended targets of this procedure, which is carried out with great precision. The HIV glycoprotein gp120 binds to CD4 receptors on CD4 cells' surfaces at this point. In order for the virus to enter the host cell, this binding relationship must be quite particular. A series of steps culminates in membrane fusion, which permits the viral genetic material to reach the host cell cytoplasm, after HIV binds to CD4 receptors. Viral envelope glycoproteins, especially gp41, undergo structural rearrangements that aid in this fusing process. Due to these alterations, the viral envelope may fuse with the host cell membrane, allowing the virus to enter the cell. In order to weaken the host immune system, HIV uses its binding stage specificity to attack immune cells. It is possible to intervene therapeutically at this period as well (HIV info, 2020).

A class of drugs called entry inhibitors may stop the HIV virus from infecting a person by blocking the contact between the virus and its receptors. Research into the complexities of viral binding may lead to the development of new antiretroviral medications that target this essential stage of the HIV life cycle.

2.1.3 Fusion Stage

The second stage of the HIV lifecycle is the fusion stage. Before infecting and attaching to CD4 cells—crucial parts of the immune system—the HIV virus binds to a receptor known as CD4 during the fusion stage of its life cycle. The CD4 receptor is one of the surface components on CD4 cells that the HIV virus has adapted to bind with. When it comes to coordinating immune responses, CD4 cells, and especially T-helper cells, are crucial (Guedán et al., 2021). They are able to recognize and bind to certain proteins, such as the HIV surface glycoprotein gp120, thanks to a molecule called CD4 that is expressed on their surface. The molecular level "identification" happens when viral proteins bind to the CD4 receptor in a certain way. A highly selective and affinity-driven binding of the viral glycoprotein gp120 to the CD4 receptor has been observed. Gp120 alters its structural composition after binding to the CD4 receptor, enabling it to engage in co-receptor interactions with other cell surface receptors such CCR5 and CXCR4. Interactions like these cause the viral protein gp41 to undergo additional modifications, which in turn cause fusion peptides to be inserted into the cell membrane. Interactions like these cause the viral protein gp41 to undergo additional modifications, which in turn cause fusion peptides to be inserted into the cell membrane. Initiating fusion between viral and cellular membranes, these peptides serve to anchor the two. A pore is created when the viral and cellular membranes merge due to more gp41 rearrangements; this allows the viral genetic material to enter the cell (Sattler et al., 2018).

In order for the viral genetic material to enter the host cell and start the replication process, the fusion pore is essential. At the point where the viral and cellular membranes fuse, a temporary hole called the fusion pore is formed. The viral core, comprising the viral genetic material (RNA), is able to enter the host cell's cytoplasm via this fusion hole. Viral components may be transported from the outside world into the host cell via the fusion pore. Everything from the viral RNA genome to the proteins and enzymes needed for the next step of the viral life cycle is part of this. Upon entering the cytoplasm, viral RNA is used as a blueprint for the replication of viral DNA by means of a mechanism known as reverse transcription. The fusion pore is dynamic and transitory in nature as it forms. It opens for a short time to let viral components in, and then it shuts again to keep cellular contents within (Zaitseva et al., 2017).

Viruses may infect host cells more or less effectively depending on the fusion pore's size and length. A pore is created when the viral and cellular membranes merge due to more gp41 rearrangements; this allows the viral genetic material to enter the cell. The viral replication and infection mechanisms are encoded in this genomic material. As a result, the fusion stage is an essential part of the HIV life cycle because it enables the virus to infect specific cells. The fusion stage is particularly crucial to the cycle because of the following reasons. It is a key step in infectivity and viral replication inside the host cell is fusion, which occurs when the viral envelope fuses with the host cell membrane and permits the viral core, which contains the genetic material, to enter the host cell cytoplasm. The cellular tropism of HIV is determined in large part by the fusion stage. When fusing with the cell membrane, various HIV strains may employ distinct co-receptors, for example CCR5 and CXCR4 (Lederman et al., 2006).

Because of these differences in co-receptor use, HIV may infect different kinds of cells. Viral tropism and the particular cell types targeted by various HIV strains may be better understood by delving into the mechanics of fusion. In terms of HIV pathogenesis and disease development, fusion efficiency is an important factor to consider. The fusogenicity of HIV strains may be impacted by variations in viral envelope glycoproteins, namely gp120 and gp41. These variations in turn influence the kinetics of viral entry and replication. Treatment plans and illness management become more complicated when certain mutations in the viral envelope glycoproteins provide resistance to entry inhibitors. Antiretroviral medication has the fusion stage as its primary therapeutic target (Yoon et al., 2019).

To prevent viruses from entering host cells and infecting them, entrance inhibitors like fusion inhibitors and co-receptor antagonists work by interfering with the fusion process. There is now an extra tool in the toolbox for managing HIV replication and disease progression—drugs that target this stage to prevent viral entrance into cells.

2.1.4 Reverse Transcription Stage

The third stage of the HIV cycle is the reverse transcription stage. The HIV virus secretes its genetic material, RNA, after it has infiltrated the CD4 cell. An essential enzyme known as reverse transcriptase begins to function inside the cell. Multiple critical steps in the HIV life cycle rely on the enzyme reverse transcriptase (Larsen et al., 2020).

First, it employs a process known as reverse transcription to transform the virus's genome from single-stranded RNA to double-stranded DNA. Incorporating viral genetic material into the genome of host cells requires this conversion. Furthermore, using the viral RNA as a template, reverse transcriptase creates a cDNA strand and then catalyses the production of a second strand of DNA that is complementary to the first (Rojas and Park, 2019).

A double-stranded DNA molecule called proviral DNA is formed during these steps; it is essential for the virus to integrate into the genome of the host cell. The viral RNA template is degraded during cDNA creation by reverse transcriptase, which also contains RNase H activity. The problem is that it isn't proofread very well, so it creates mistakes that add to genetic variety and make HIV drugs harder to treat. This is accomplished by reverse transcriptase, which uses the viral RNA as a template to synthesise a complementary DNA strand. The end product of this procedure is a DNA molecule with just one strand, the minus (-) strand. The next step is for reverse transcriptase to create a second DNA strand that is complementary to the first. This process creates proviral DNA, a molecule with two strands of DNA (Ma et al., 2022).

In order for the virus to insert its genetic code into the host cell's genome, this freshly produced DNA is crucial. After the virus has fully integrated into the host cell, it may replicate itself by controlling the host cell's machinery to make new viral particles. Thus, HIV life cycle components that allow the virus to infect host cells in a sustained manner include reverse transcription. In order to establish a long-term infection, the virus must first prepare itself for integration into the host's DNA, which it does during the reverse transcription stage of HIV infection. There are no outward signs of the reverse transcription process at this minuscule level. Although there are no outward signs of reverse transcription, the actions it facilitates, such the virus's growth and dissemination, may cause a gradual decline in immune function. For several reasons, the HIV life cycle's reverse transcription step is critical. In the first place, it helps the infection get started by letting the virus turn its RNA into DNA, which it may then incorporate into the genome of the host cell. Because it prepares the groundwork for a chronic, and often lifetime, infection, this integration is crucial (Sattler et al., 2018).

Antiretroviral treatments often target the virus directly during its active replication phase, but after the viral DNA is integrated, it may stay inactive or latent, allowing the virus to elude the host's immune system. There is a high mutation rate because reverse transcription is error-prone and the reverse transcriptase enzyme does not have proofreading capabilities (Chen, 2019). This genetic diversity has two sides: on one hand, it helps the virus adapt rapidly, which makes it more resistant to drugs and immune responses, and on the other hand, it lays the groundwork for the virus to be vulnerable to targeted therapies. Reverse transcriptase inhibitors, in particular, are among the antiretroviral medications that target reverse transcription. By interfering with this vital step, these medications hinder the virus's capacity to replicate its genetic material and propagate to new hosts. Inhibiting this stage is crucial for HIV therapy and management since it significantly affects the disease's course and the risk of transmission (Chen, 2019).

2.1.5 Integration Stage

The fourth stage is the integration stage. An essential part of the HIV life cycle, integration occurs when the viral DNA is inserted into the genomic DNA of the host cell. The viral protein integrase is essential for HIV replication and plays a vital role in this process. In order for the HIV genome to be integrated into the host DNA, an enzyme known as integrase must be present throughout the replication cycle of the virus (Wu et al., 2021).

Prior to integration, this enzyme performs 3'-end processing, which involves cutting a small number of nucleotides off the 3' ends of the viral DNA. Because it makes the sticky ends needed for the next processes, this preparation is crucial. One of integrase's primary roles is to facilitate the incorporation of viral DNA into the host genome. The first stage in its two-part process is to catalyze a strand transfer reaction, which involves cutting the host DNA at specified sequences. This leaves open spots where the viral DNA may be inserted. Then, integrase helps the viral and host DNAs connect, and the virus becomes a provirus inside the host's genome. The proviral DNA is eventually incorporated into the host cell's DNA and replicates alongside the host cell's DNA when the cell divides. Integrase further works in tandem with the host cell's DNA repair systems to identify and fix the integration sites, making sure the viral DNA remains stable and permanently integrated into the host genome (Yoon et al., 2019).

Crucial to HIV integration, the process involves complex interactions between viral components and host cell machinery as freshly produced viral DNA is transported into the host CD4 cell nucleus. The HIV-RNA is not transported into the nucleus in isolation after cytoplasmic reverse transcription produces double-stranded DNA. The complex it generates is called the pre-integration complex, or PIC. The viral DNA must be protected and transported into the nucleus with the help of the PIC. Along with the viral DNA, it contains a number of viral proteins, such as matrix and integrase proteins, and maybe other viral and cellular components. In the early stages of PIC formation, the matrix protein p17 is believed to have a stabilizing function. At this step, integrase plays a crucial role in maintaining the integrity of the viral DNA, which is necessary for integration into the host genome (Guedán et al., 2021).

Throughout HIV's life cycle, viral proteins are involved in a wide variety of important processes, including entrance, replication, and budding. For the virus to replicate, each of its proteins must perform a specific role. It is quite probable that the host cell's nuclear import machinery is involved in the intricate process of PIC transport across the nuclear membrane (Guedán et al., 2021).

In order to translocate the PIC into the nucleus, HIV makes use of the host cell's own nuclear import mechanisms. Proteins such as importing, which are typically involved in the process of cellular protein import into the nucleus, are taken over to aid in this endeavour. These proteins help the viral proteins linked to the PIC, especially integrase, get through the nuclear pore complex by recognizing their nuclear localization signals (NLS). The virus has to find a way through the nuclear membrane in cells that aren't dividing, and it accomplishes so by entering the nucleus via a specific opening. The PIC and other big molecules and complexes may enter the nucleus via these holes. The complex is guided through the nuclear pore by the host's import machinery, which mediates the contact between the PIC and the pore (HIVinfo, 2020).

After entering the nucleus, the PIC is ready to start incorporating its viral DNA into the genome of the host cell. The capacity of HIV to instal a long-term infection hinges on how it handles this transport—namely, how efficiently and covertly the viral DNA reaches the host genome, avoiding degradation by cellular defences. One evidence of HIV's evolutionary adaptation to humans is the virus's capacity to use the host's nuclear import system (HIVinfo, 2020).

Third-end processing is the first step that Integrase takes. Removing a small number of nucleotides from the 3' ends of the viral DNA double strand is the next stage. As a result, the viral DNA ends become what are called "sticky ends" or cohesive ends. The next integration phase relies on these sticky ends. Integrase maintains tight control over the 3' end nucleotide removal process to guarantee accurate processing of the ends. This procedure helps the viral DNA integrate into the host genome more securely by making sure it is compatible with the host cell's DNA (HIVinfo, 2020).

The specificity of integration is further enhanced by the development of these sticky ends. Integrase is able to adhere to particular sequences in the host DNA, called attachment sites or integration sites, by using the sticky ends as guides. For several important parts of the HIV life cycle and its host interaction, the integration stage is pivotal. First, a long-term, chronic infection may be established when the viral DNA becomes a permanent part of the host cell's genome. This process is called integration. Through this integration, the virus is able to replicate and infect more cells, leading to the spread of HIV both inside the host and to other people (Sattler et al., 2018).

Latent infections may also develop as a result of integration; in these cases, the virus stays inactive inside the host cell and does not actively generate new viral particles. The ability of these dormant viral reservoirs to avoid immune surveillance and antiretroviral treatment is a major obstacle to the elimination of HIV. Additionally, HIV's genetic variety is enhanced by integration, which aids in the virus's evolution and the development of resistance to antiretroviral medications and immune response evasion (Sattler et al., 2018).

Because it is an essential part of the HIV life cycle, antiretroviral medication aims to block the integrase enzyme, which stops viral DNA from integrating into the host genome. Therefore, in order to create innovative antiretroviral treatments and efficient methods for controlling and managing HIV infection, it is crucial to comprehend the significance of integration (Eggleton and Nagalli, 2020).

2.1.6 Replication

The fifth stage of the HIV lifecycle is known as replication. There are a number of complex processes that lead to the creation of new virus particles during the replication stage of the HIV life cycle. The viral DNA, or provirus, is used as a template for transcription by the RNA polymerase machinery of the host cell once it has integrated into the host cell's genome. In order to synthesise viral RNA molecules, RNA polymerase commences transcription upon recognising certain promoter regions within the proviral DNA (Crater et al., 2022).

Step one in the HIV life cycle's replication stage is the identification of certain promoter sequences within the integrated viral DNA. The viral DNA that is integrated into the host cell has particular DNA sequences called promoters that act as recognition sites for the RNA polymerase machinery of the host cell. In order to start transcription, RNA polymerase attaches to certain areas found in promoters. The HIV genome includes promoter sequences that enable transcription in the long terminal repeat (LTR) regions that surround the integrated proviral DNA. The process begins with the binding of the viral DNA template strand to the promoter regions, and then the RNA polymerase machinery in the host cell unwinds the DNA double helix to start transcription. This starts at the promoter region's transcription start point and moves along the viral DNA template strand. When RNA polymerase moves along the viral DNA template, it adds nucleotides in a 5' to 3' direction to synthesise a corresponding RNA transcript, a process known as elongation of the RNA transcript (Guedán et al., 2021).

The viral DNA template contains nucleotides that are complementary to the ribonucleoside triphosphate (NTP) substrates used to synthesise the RNA transcript. Messenger RNA (mRNA) transcripts are produced after the parent RNA transcript, which has been synthesised, passes through a series of processing processes. Polyadenylation, splicing, and capping are all parts of the processing procedure. A 5' methylguanosine cap is added to the mRNA during capping, which shields the transcript from degradation and makes translation easier. The process of splicing isolates the parts of the main RNA transcript that code for proteins by removing non-coding sections, known as introns. The 3' end of messenger RNA (mRNA) is stabilised and its translation is regulated by adding a string of adenine nucleotides, known as a poly-A tail, by polyadenylation (Zaitseva et al., 2017).

Mature messenger RNA transcripts leave the cell nucleus and go into the cytoplasm, where they are used as building blocks for proteins by the ribosomes in the host cell. At different points in the HIV life cycle, structural proteins like Gag, Pol, and Env, and regulatory proteins like Tat and Rev are synthesised from the genetic information carried by the messenger RNA transcripts. Splicing and polyadenylation are two of the processing processes that the freshly transcribed viral RNA goes through in order to produce mature messenger RNA (mRNA) transcripts. (Yoon et al., 2019). While polyadenylation adds a string of adenine nucleotides (poly-A tail) to the 3' end of messenger RNA (mRNA), splicing removes non-coding sections (introns) from the main RNA transcript. The stability and effective translation into proteins of the mRNA molecules are guaranteed by these alterations. When a virus matures, its messenger RNA (mRNA) transcripts leave the nucleus and go into the cytoplasm, where they may be used as building blocks for new proteins. The viral machinery, which consists of structural proteins like Gag, Pol, and Env and regulatory proteins like Tat and Rev, is constructed from viral mRNA by the ribosomes in the host cell (Yoon et al., 2019).

the assembly, budding, and replication phases of a virus's life cycle, several viral proteins are crucial. Immature viral particles are formed when freshly synthesised viral proteins and RNA molecules combine in certain cellular compartments, such as the cell membrane or the endoplasmic reticulum. The Gag polyprotein is an essential assembly regulator, directing the viral core's development and the integration of viral RNA (HIVinfo, 2020).

In order for the virus to grow into an infectious particle, it must first go through a sequence of stages. In this step, the viral protease enzyme splits the Gag and Gag-Pol polyproteins, which causes the core of the virus to reorganise itself and separate into its component proteins. Budding is the process by which the host cell releases the mature virus particles. When the virus is ready to release its particles into the body, it buds off the host cell membrane and takes on a lipid envelope that is similar to its own. Incorporating host cell proteins, such as CD4 and co-receptors, into their envelopes, the viral particles undergo budding (HIVinfo, 2020). Now that the virus has been unleashed, its infectious particles may infect nearby CD4 cells, continuing the viral replication cycle (HIVinfo, 2020).

The stage of replication is important for several reasons. The replication stage enables propagation of viruses which involves making copies of the virus in order to replicate and spread to other cells in the host organism. The human immunodeficiency virus (HIV) manufactures new infectious viral particles by encroaching on the machinery of the host cell and replicating its genetic material and viral proteins. The formation of a chronic infection and the systemic dispersion of HIV throughout the body are both aided by this continual replication cycle. The development of HIV infection and its subsequent phases, including acquired immunodeficiency syndrome (AIDS), is closely associated with the virus's replication. As the immune system weakens over time due to unchecked viral replication, the host becomes more susceptible to opportunistic infections and cancers, which are hallmarks of AIDS (Chen, 2019).

In order to reduce HIV replication, maintain immune function, and prevent disease progression, antiretroviral treatment (ART) primarily aimed at reducing viral replication. Despite antiretroviral therapy (ART), HIV may continue to replicate and build latent reservoirs of infected cells that are able to avoid immune monitoring. Infected cells that are in a dormant state have proviral DNA but are not actively releasing virus particles. The ability of these reservoirs to reawaken and restock the viral population in the event of a treatment interruption makes them a formidable obstacle to HIV eradication efforts (Guedán et al., 2021).

In order to devise methods to target and eradicate latent reservoirs, it is essential to comprehend the processes of viral replication and latency. The replication stage is a key factor in the genetic variety and development of HIV, which in turn leads to drug resistance. Viruses produce a wide variety of variations during replication, each with its own fitness level and level of resistance to antiretroviral medication (Guedán et al., 2021).

When therapy fails and drug-resistant strains evolve, it's because certain mutations make the virus resistant to certain antiretroviral drugs. Optimising treatment regimens and minimising the development of medication resistance requires monitoring viral replication dynamics and genetic heterogeneity. As a key component of HIV infection control, the replication stage is an ideal target for therapeutic intervention (Rossi et al., 2021).

In order to reduce viral load and decrease replication, antiretroviral medications block many components of the replication cycle, including reverse transcription, integration, and viral maturation. Restoring immunological function, improving health outcomes, and prolonging life in HIV-positive persons are all aided by antiretroviral therapy (ART), which reduces viral replication to undetectable levels. The rapid mutation rate that occurs during HIV replication causes genetic diversity among viral populations, which in turn increases the likelihood of drug resistance (Rossi et al., 2021). Because of this genetic heterogeneity, drug-resistant HIV strains may arise and make antiretroviral medications less effective. In order to create novel antiretroviral treatments that can successfully target drug-resistant viruses, it is crucial to understand the replication mechanism.

2.1.7 Assembly

The sixth stage of the HIV lifecycle is the assembly stage. An important portion of the HIV life cycle occurs during assembly, when the virus's freshly produced parts assemble to create immature viral particles. Before the virus can be assembled, its constituent parts are synthesised by the machinery of the host cell. The viral RNA, structural proteins (Pol, Env, and Gag), and regulatory proteins (Tat and Rev) make up these parts (Cann, 2018).

Protein synthesis machinery inside the host cell coordinates the transcription and translation of the viral genome, which in turn synthesises these components. In the process of assembling viral components into immature viral particles, the Gag polyprotein is important. The viral protease enzyme separates the monopeptide chain that makes up gag during synthesis into its component structural proteins: the matrix (MA), the capsid (CA), and the nucleocapsid (NC). Through Gag-mediated specialised protein-protein and protein-RNA interactions, these structural proteins self-assemble at the host cell's plasma membrane. When Gag assembles at the plasma membrane, it comes into contact with freshly produced viral RNA molecules that are encapsulated inside the virion. This interaction leads to the incorporation of viral RNA (Crater et al., 2022).

In order to selectively incorporate the viral genome into the forming virion, Gag's nucleocapsid (NC) domain attaches to particular packaging signals within the viral RNA. Once the virus has completed assembly, its immature particles may acquire a lipid envelope from the host cell membrane by "budding" from the cell membrane. In budding, the viral components are encased in the lipid bilayer, creating a virion with the viral components contained inside. At this point, the assembly step is complete, and the virus's immature particles are released into the extracellular space. The assembly stage is important in the HIV cycle for the following reasons. During the assembly stage, freshly synthesised viral components assemble to create immature viral particles, which are infectious. In order for the virus to infect both hosts and other people, these particles are crucial (Crater et al., 2022).

The virus can't replicate or infect new hosts unless it can assemble properly. The process of viral replication and dissemination occurs when the virus's components are assembled into immature particles. This process enables the virus to replicate and spread inside the host organism. After assembling, the virus's immature particles emerge from the host cell's membrane and enter the extracellular environment. The viral replication and dissemination cycle may be sustained when these particles infect nearby cells. Incorporating structural proteins (including Gag, Pol, and Env) and regulatory proteins, together with viral RNA, into the viral particles occurs during assembly. Their ability to infect and replicate depends on the viral particle makeup, which includes viral RNA. The assembly stage plays a role in viral tropism, which is the process by which the virus learns which cell types it can infect (Goulding, 2023).

The cell types that the virus may infect are determined by the proteins that are assembled into the viral envelope. These proteins include CD4 and co-receptors, among others. Viruses may infect hosts more efficiently when they assemble at points of cell-cell contact, which allows them to transmit from cell to cell (Guedán et al., 2021). Antiretroviral treatment (ART) may be able to target the assembly stage of the virus. Inhibitors of maturation or entrance, which are drugs that disrupt viral assembly or budding, may reduce viral replication and the creation of infectious viral particles. Novel antiviral medications targeting this stage of the HIV life cycle need an understanding of the mechanics of assembly (Guedán et al., 2021).

2.1.8 Budding

The very final stage of the HIV lifecycle is known as budding. An essential element of the HIV life cycle, budding occurs when the host cell membrane releases freshly produced viral particles, enabling the virus to infect neighbouring cells. The host cell must first produce viral RNA and proteins like Gag, Pol, and Env before budding can take place. The process of budding cannot begin until the host cell has synthesised viral RNA and viral proteins, including structural proteins like Pol, Env, and Gag (Garoff et al., 2019).

The host cell stores these components and sends them to certain locations on its membrane. A process called assembly of viral components into budding virions occurs when viral proteins, including the Gag polyprotein, engage with cellular factors and lipid rafts at precise locations on the inner leaflet of the host cell membrane. When it comes to the assembly process and the production of immature viral particles, gag is king. A well controlled procedure guarantees that every virion includes the genetic material needed for replication by incorporating viral RNA into the assembly of HIV viral particles. This happens when the Gag polyprotein interacts with certain Ψ elements in the viral RNA genome (HIVinfo, 2020).

The structural protein Gag has RNA binding domains that can identify and bind to the elements, making it easier for the viral RNA to be packaged selectively. Incorporating Gag-viral RNA complexes into building viral particles guarantees that every virion carries replication-specific genetic material as assembly occurs. During the production of mature viral particles, the viral genome is stabilised and kept intact by enclosing it inside the viral core. Once the viral particles are created, they undergo a process called budding, where they emerge from the host cell membrane (HIVinfo, 2020).

The viral particles take on a lipid sheath that is produced from the host cell membrane when they undergo budding. During budding, viral particles are detached from the host cell membrane and then condense into spherical forms with a viral core encased in a lipid envelope. When viruses undergo budding, they take on the proteins of host cells, such as CD4 and co-receptors, and integrate them into their envelopes. These proteins from host cells may have already been on the plasma membrane while the virus was budding, or they might be actively brought in and integrated into the viral envelope as the virus is budding. Virus tropism and infectiousness may be affected by host cell proteins on the viral envelope. When budding is complete, the virus's mature particles are discharged into the extracellular area via the host cell membrane. These fully developed viral particles may now infect other cells, continuing the viral cycle of replication and spread (Battistini Garcia & Guzman, 2021).

In the HIV life cycle, the budding stage is vital for several reasons. First, it's the last stage before the immature virus particles are assembled and released from the host cell, which makes them infectious. This is because these virions may infect new cells, which allows the virus to spread all throughout the host and even to other people. Another factor that might affect the viral particles' infectivity and tropism is the incorporation of host cell proteins into their envelopes during budding. Additionally, antiretroviral medications that target the budding process may decrease viral replication, making it a possibly therapeutic target. Budding also reduces the number of CD4+ T cells and hinders immunological function, which are factors in viral pathogenesis and the development of illness. Finally, viral reservoirs may be established inside hosts when the virus efficiently transmits from cell to cell via budding at regions of cell-cell contact (Lederman et al., 2006).

2.2 Immunology of HIV infection

Human Immunodeficiency Virus (HIV) infection remains a global health challenge, affecting millions of individuals worldwide. The interplay between the virus and the immune system is complex, with HIV evading host defenses and progressively undermining immune function. This literature review aims to explore the current understanding of the immunology of HIV infection, focusing on key aspects such as viral entry, immune responses, immune evasion mechanisms, and implications for therapeutic strategies (Goulding, 2023). Viral Entry and HIV primarily targets CD4+ T lymphocytes, macrophages, and dendritic cells, exploiting their surface receptors for viral entry. The viral envelope glycoprotein, gp120, interacts with CD4 receptor and chemokine receptors (e.g., CCR5, CXCR4) to facilitate viral attachment and fusion. Understanding these interactions has led to the development of entry inhibitors targeting these receptors as a therapeutic approach to prevent viral transmission (Mazzon & Marsh (2019).

Upon HIV exposure, the immune system initiates both innate and adaptive responses to control viral replication. Innate immune cells such as natural killer (NK) cells and macrophages recognize and eliminate infected cells through cytotoxic mechanisms and cytokine secretion. Meanwhile, adaptive immune responses involve antigen presentation by dendritic cells, activation of CD4+ T-helper cells, and cytotoxic CD8+ T cell-mediated clearance of infected cells (Larsen et al., 2020). Neutralizing antibodies also play a crucial role in limiting viral spread and preventing reinfection. Despite host immune responses, HIV employs various strategies to evade detection and elimination. These include rapid mutation rates leading to viral diversity, downregulation of major histocompatibility complex (MHC) molecules on infected cells, and interference with antigen presentation pathways. Additionally, HIV can establish latent reservoirs in resting CD4+ T cells, evading immune surveillance and antiretroviral therapy (Larsen et al., 2020).

Understanding the immunological mechanisms of HIV infection is critical for the development of effective therapeutic interventions. Current antiretroviral therapies (ART) target different stages of the viral lifecycle, suppressing viral replication and preserving immune function. Additionally, strategies aiming to boost immune responses, such as therapeutic vaccination and immune checkpoint inhibitors, are being explored to achieve viral control and possibly functional cure (Hoogeveen and Boonstra, 2020).

The immunology of HIV infection involves a complex interplay between the virus and host immune system, with ongoing efforts to decipher these interactions for therapeutic advancements. Further research is needed to elucidate immune evasion mechanisms, identify correlates of protection, and develop innovative strategies towards achieving long-term control or eradication of HIV infection (Garoff et al., 2019)

2.3 Characteristics of the Immune System

The immune system has the function of protecting the body against infectious agents, consisting of cells, tissues and molecules (Sharon J, 2000) is divided into primary and secondary lymphoid organs. Leukocytes known as white blood cells are the immune cells of the body, among these are the CD4 + T lymphocytes that are produced in the thymus and are responsible for organizing and command responses by the actions of aggressors (Ministério da Saúde, 2014) (Santos C et al., 2007). Immunity can be natural or acquired, natural, presents defense against microorganism, with an initial line of defense, having biochemical and cellular defense mechanisms and is programmed to act quickly to infections. The adaptive immune response or have acquired the ability to remember, responding in cases of repeated exposure to more aggressively when a microorganism is known, and have specificity for different molecules, having as main components lymphocytes **(**Abbas, Lichtman and Pillai, 2011**)**.

The acquired immune response has two types, humoral immunity and cellular immunity. Known as humoral, that is mediated by molecules present in the blood and mucosal secretions, called antibodies, which are produced by B lymphocytes by T-lymphocyte mediated cellular immunity acts on intracellular microorganisms such as some bacteria and viruses causing the destruction of these or of infected cells, promoting the removal of reservoirs of infection **(**Abbas, Lichtman and Pillai, 2011**)**. In acquired immunity there are three main cellular types involved in this process: T cell that matures in the thymus, cell B is mature in the bone marrow and a third type known as antigen-presenting cell (APC) such as macrophages and dendritic cells the these interact in a complex manner to the immune response that occurs as a whole (Coico and Sunshine, 2010) (Benjamini, Coico and Sunshine, 2002)

2.4 Immunological characteristics of the HIV

In addition, to the high affinity of the viral glycoprotein gp120 to cellular receptors, especially CD4, it is necessary a group of chemokine receptors, which act as a coreceptor for HIV, are known as the principal chemokine receptor type 5 (CCR5) and receiver chemokine type 4 (CXCR4), they facilitate viral entry into the cell (Ferreira, Riffel and Sant'Ana, 2010; Sharon, 2000). The CD4 + T lymphocytes are considered target cells from infection by HIV, they have high levels of CD4 and expressing co receptor. There are also other types of cells that can be infected by HIV, they express low levels of CD4 and co receptor are known as macrophages, dendritic cells and microglia cells (Abbas, Lichtman and Pillai, 2011; Ferreira, Riffel and Sant'Ana, 2010; Sharon, 2000). This binding of gp120 to the receptor and co receptor allows a domain of viral glycoprotein gp41 inducing fusion of the virion to the target cell cytoplasm, leading to release of the core of HIV to the cytoplasm of the host cell, initiating the viral reproductive cycle (Santos, Albuquerque and Brito, 2014).

In the cytoplasm of the cell, the viral RNA is retrotranscribed into a double-encoded DNA strand (cDNA), i.e. by the enzyme reverse transcriptase. Subsequently the cDNA binds to viral and cellular proteins to form a nucleoprotein pre-integration complex, which goes into the cell nucleus. The viral integrase enzyme also adheres to the core catalyzing the coupling of the viral cDNA into the genome of the host cell. Thus the integrated cDNA is now called provirus, may remain idle for a specified time, with little or no production of viral protein. This process occurs in individual cells seemed to be CD4 + memory T cells and macrophages sleepers, yielding the latent form of the virus (Abbas et al., 2011; Murphy et al., 2010; (Ferreira et al., 2010; Santos et al., 2014).

To place the transcription of HIV provirus the presence of its long terminal repeats necessary, known as long-terminal repeats (5'LTR) where a gene promoter and enhancer sequences; also necessary to make the sequences that collaborate in polyadenylation, located in 3'LTR. In the promoter are ligated cellular transcription factors NF-kB (nuclear factor kappa B) and (SP1 selective promoter factor 1) to be transcriptional activation. However, this transcript only becomes present when there is activation of T cells and macrophages. After activation few full-length transcripts are formed in the core, they produce messenger ribonucleic acid (mRNA) encoding regulatory proteins, and even transported from the nucleus to the cytoplasm of the cell, where they are translated. As for the structural proteins, they are produced from the accumulation of regulatory proteins in the nucleus (Abbas et al., 2011; Murphy et al., 2010; Ferreira et al., 2010; Santos et al., 2014).

Like other retroviruses, HIV has three main structural proteins. Its proteins as described here, are responsible for most of their origin, they are known as gag (group-specific antigen), pol (polymerase) and env (envelope), such proteins have the function, respectively, encoding the viral proteins of the viral core, production of enzymes that assist in replication and integration of the virus and finally the envelope glycoprotein production. There are also six other genes encoding proteins and contribute to the regulation of viral replication and infectivity are classified as regulatory genes Tat (transactivator) and Rev (regulator of viral expression) essential for viral replication and transported to the nucleus by binding to HIV RNA. The Tat protein will join the 5 'end of the transcript of HIV, and cellular factors, accelerating to 1000 times the full production of transcripts. Have the Rev protein binds to the isolated transcripts or unprocessed allowing your core output (Abbas et al., 2011; Murphy et al., 2010); Ferreira et al., 2010; Santos et al., 2014). The HIV genome also encodes the accessory proteins, Nef (negative regulatory factor), vif (viral infectivity), Vpr (Viral protein R) and Vpu (U viral protein) responsible for efficient virus production (Abbas et al., 2011; Murphy et al., 2010; Ferreira et al., 2010; Santos et al., 2014).

The structural genes have long polypeptide chains produced by mRNA, which is subsequently cleaved by viral protease into mature proteins in the cytoplasm. The result of the cleavage of Gag gene are four proteins: CA (capsid, p24), MA (matrix, p17), NC (nucleocapsid p7) and p6; have the env gene produces glycoproteins, gp120 and gp41, these are structured as trimers in the viral envelope. Finally, the cleavage of the pol gene, which will result in the formation of three proteins essential for virus multiplication, are also known as p11, p66/ p51 and p32, are found in the same protease enzymes, reverse transcriptase and integrase respectively. The proteins mentioned organize and form the cores of HIV which undergo sprouting containing the glycoproteins gp41 and gp120 in the plasma membrane resulting in the HIV virion, is released from the host cell into the surrounding medium, which may or may not infect new cells (Murphy et al., 2010; Ferreira et al., 2010; Sharon, 2000).

Clinical manifestations (signs & symptoms) of HIV and AIDS

The signs and symptoms for HIV and AIDS vary from stage to stage and from an individual to the next. When a person contracts HIV, the virus enters their body and starts replicating quickly during the first infection, which is also called acute HIV. This first stage usually occurs between two and four weeks after being exposed to the virus. At this point, some people may start to feel sick with the flu, while others may feel perfectly well. Acute HIV infection symptoms might last anywhere from a few hours to a few days. Common symptoms include a high temperature, headache, muscular pains, rash, sore throat, enlarged lymph glands, diarrhoea, decreased appetite, coughing, and night sweats (Guedán et al., 2021). These signs and symptoms are so similar to the flu and other viral infections that people often mistake them for something else. But, testing for HIV infection should be initiated upon the existence of these symptoms, especially when they occur in conjunction with recent high-risk behaviour or exposure to the virus (HIVinfo, 2020).

Acute HIV infection may not always cause symptoms in all people. Some people may not have any symptoms at all, or their symptoms may be so subtle that no one notices them. Even though there are no outward signs of infection, the virus is still quite infectious since the viral load in the blood is usually rather high at this point (HIVinfo, 2020). Acute HIV infection must be detected as soon as possible for many reasons. First, antiretroviral medication (ART) may help reduce viral replication, maintain immune function, and enhance long-term results; it is most effective when started promptly after an HIV infection is identified and diagnosed at this stage (HIVinfo, 2020). People who get an HIV diagnosis while they're in the acute phase of the disease may take measures to stop the spread of the virus by notifying their sexual partners of their possible exposure to the virus and engaging in safer sexual practices (HIVinfo, 2020).

The clinical latent stage is the one that follows. Chronic HIV infection, or clinical latent infection, is characterised by ongoing viral replication and immune system dysfunction, with a focus on CD4+ T cells—an essential cell type for immune response coordination—as a primary target. Many people at this stage of the virus's life cycle may not show any outward signs of infection or symptoms, even if the virus is still replicating (Battistini Garcia & Guzman, 2021). People who aren't taking antiretroviral medication (ART) may remain in the clinical latent infection stage for decades. During this period, the virus slowly weakens the immune system's capacity to fight against infections; however, for some people, this process may be sluggish and symptomatic (Chen, 2019). One thing to keep in mind is that people might have vastly different rates of illness development; some people may have more severe symptoms or problems at an earlier stage than others. Even though many people living with HIV don't feel any symptoms, it's nevertheless suggested to check CD4+ T cell counts and viral load levels often to see how the illness is progressing and whether antiretroviral therapy (ART) has to be started. Moreover, at this point in time, some people may have moderate or nonspecific symptoms including lethargy, minor infections, or chronic generalised lymphadenopathy (enlarged lymph nodes), which might lead to additional HIV testing and assessment (Chen, 2019).

During the clinical latent infection stage, early detection and care of HIV infection are essential for preventing disease progression, reducing the risk of opportunistic infections, and improving long-term results. Appropriate antiretroviral therapy (ART) may lessen the likelihood of HIV-related problems and transmission to others by reducing viral replication, maintaining immune function, and starting treatment quickly A person may proceed from a clinical latent stage of HIV infection to a symptomatic stage, or symptomatic HIV illness, as the infection advances. As the virus keeps replicating and the immune system becomes weaker, symptoms and clinical manifestations start to show up during this phase (HIVinfo, 2020).

The symptoms that may manifest are as follows. Inflammation and immunological activation caused by HIV infection may lead to fever, which can be persistent or recurring. Other symptoms, such lethargy, malaise, and night sweats, could accompany a fever. Excessive tiredness is a typical symptom of HIV infection and it may greatly affect one's wellbeing. Multiple reasons may contribute to fatigue, including as the virus's direct impact on the body, the activation of the immune system, and psychological stress. Enlargement of lymph nodes, or lymphadenopathy, is a characteristic sign of symptomatic HIV infection and is characterised by swollen lymph nodes. Tender or painless swollen lymph nodes, especially in the neck, armpits, or groyne, can indicate that your immune system is fighting against HIV or another infection. Individuals with symptomatic HIV infection may have chronic or recurring diarrhoea as a gastrointestinal symptom (Cann, 2018).

Opportunistic infections, HIV-related enteropathy, and drug side effects are all potential causes of diarrhoea. Unintentional weight loss is a major worry in people with symptomatic HIV infection. It may be caused by a number of things, including as a lack of hunger, problems with absorption, changes in metabolism, and other illnesses. Fungal infections of the mouth (throush): People living with HIV are at increased risk for developing candidiasis, an infection of the oral cavity caused by Candida species. White or creamy patches might appear on the inside of the cheeks, the tongue, or the throat when you have oral thrush. You can also feel some pain or discomfort. Reactivation of the varicella-zoster virus, more often known as shingles, is more likely in people with compromised immune systems, such as those who are HIV positive. Painful blisters packed with fluid run along a dermatome; tingling or burning may be present before the rash of shingles appears. Opportunistic pathogens like Pneumocystis jirovecii (also known as Pneumocystis pneumonia or PCP) are a leading cause of HIV-associated pneumonia, sometimes known as pneumonia.

Acquired Immunodeficiency Syndrome (AIDS) may develop from a persistent HIV infection if the virus is not treated. People with AIDS have a severely compromised immune system, making them more likely to get opportunistic infections and several types of malignancies. AIDS-related infections may cause a broad range of symptoms, but some of the most common include: shaking, chills, frequent fever, constant diarrhoea, enlarged lymph glands, oral sores or white patches, extreme weakness, extreme weariness, quick weight loss, and skin rashes or bumps (Zaitseva et al., 2017).

These signs and symptoms show how the body's defences have been weakened due to the systemic effects of HIV-related immune suppression. Opportunistic infections linked to AIDS may show up in a variety of ways and impact different organ systems. As an example, a fungal lung infection known as Pneumocystis jirovecii pneumonia (PCP) may cause symptoms such as coughing, difficulty breathing, chest discomfort, and fever. Cough, fever, night sweats, lethargy, and exhaustion are some of the symptoms that may accompany tuberculosis (TB). Oral thrush, esophageal candidiasis, and vaginal yeast infections are all symptoms of candidiasis, a fungal infection. Toxoplasmosis causes neurological impairments, disorientation, seizures, and headaches, whilst Cytomegalovirus (CMV) retinitis may cause blindness or severe visual loss (Yoon et al., 2019). Furthermore, skin lesions, mouth lesions, swollen lymph nodes, fever, weight loss, and exhaustion might be symptoms of AIDS-related diseases such non-Hodgkin lymphoma and Kaposi's sarcoma (Berhan et al., (2022).

2.5 Diagnosis of HIV infection

If the virus is present or if it has affected the immune system, a number of tests may be used to confirm an HIV infection. Enzyme-Linked Immunosorbent Assay (ELISA) and other HIV antibody tests are often used to identify the presence of antibodies that the body produces in response to HIV. Essential techniques for identifying HIV infection include fast HIV antibody testing and the Enzyme-Linked Immunosorbent Assay (ELISA). The enzyme-linked immunosorbent assay (ELISA) may identify HIV-related antibodies. The procedure involves drawing blood from the patient and analysing it for antibodies that might indicate HIV infection. Because of its precision and dependability, ELISA is often used as the first screening test for HIV because of its high sensitivity (Wu et al., 2021).

A faster alternative to the usual laboratory-based ELISA assays is the rapid HIV antibody test. These tests may be done with either oral fluid or blood samples taken by fingerstick and provide results in a matter of minutes. In point-of-care settings like clinics, community health centres, or outreach programs, where prompt diagnosis and counselling are essential, rapid tests are very valuable. They make HIV testing and counselling more accessible and convenient for healthcare practitioners, who may then use these services in a wider range of contexts (Ma et al., 2022).

Early diagnosis of HIV infection is critical for HIV prevention and treatment efforts, and both the ELISA and fast HIV antibody tests are capable of doing just that. One diagnostic method that can identify both antibodies to HIV and the virus's early infection protein, the p24 antigen, is the HIV antigen/antibody combination test. Faster HIV detection and more accurate diagnosis of acute HIV infection are two of the many benefits these tests provide over conventional antibody-only assays. Rapid viral replication in the early stages of HIV infection causes an increase in viral load and the generation of the p24 antigen. Early detection of the p24 antigen in blood before the immune system produces antibodies makes it a valuable diagnostic for HIV infection (Ma et al., 2022). A single assay can detect both HIV antibodies and the p24 antigen, which is how HIV antigen/antibody combination tests function. The patient is examined by drawing blood, which is then tested either in a lab or at the point of treatment. If the p24 antigen and/or HIV antibodies are present, it means that you have recently been infected with HIV (Ma et al., 2022).

2.6 Management of HIV Infection

Managing an HIV infection involves a multi-pronged strategy to bring the virus under control, keep the immune system functioning, stop its transmission, and deal with any related health issues. Antiretroviral treatment (ART) is a cornerstone of this approach to care; it entails taking a cocktail of medications to lower viral load, decrease HIV replication, and maintain immune function (Rossi et al., 2021). The efficacy of therapy and the advancement of illness may be evaluated with the regular monitoring of important indicators including viral load and CD4 cell count. Counselling and adherence support services are essential for ART to be effective, and ART adherence is paramount. Another important part of HIV care is preventing and controlling opportunistic infections. In order to reduce the likelihood of consequences, opportunistic infections must be identified and treated promptly. Reducing the spread of HIV and preventing new infections is an essential part of HIV management regimens, and prevention programs are an essential part of that. A variety of treatments are included in these programs with the goal of lowering risk factors, increasing access to preventative resources, and encouraging safer behaviours. A comprehensive review of essential preventative services is presented here (Sattler et al., 2018).

Distributing condoms in healthcare facilities, via community groups, and through other means promotes their usage as a barrier technique during sexual activity. To lessen the likelihood of contracting HIV, people who are HIV-negative may take antiretroviral medicine as part of a program called pre-exposure prophylaxis (PrEP). In order to prevent the transmission of HIV, it is recommended to take daily oral PrEP, which usually contains tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Programs to Reduce Harm for Individuals Who Inject Drugs "PWID": Because they are more likely to share needles and injection equipment, people living with HIV are more likely to get the virus (Sundareshan et al., 2024).

Safe injection practices teaching, sterilized needles and syringes, and access to addiction treatment services are all part of harm reduction initiatives that aim to lower the risk of HIV transmission among people who inject drugs (PWID). The provision of counselling services includes instruction in safer sex practices, such as the proper and regular use of condoms, the disclosure of one's HIV status and risk factors to one's sexual partners, and the negotiation of less risky sexual activities

(Garoff et al., 2019). Specific issues or concerns pertaining to HIV prevention may be discussed in counselling sessions, which can be held either one-on-one or in groups.

2.7 Antiretroviral Therapy for Management of HIV

Antiretroviral therapy (ART) involves the use of various combinations of antiviral medications to treat HIV. There are antiviral medications that are accessible and have been effective in treating HIV infection. HAART, which stands for highly active antiretroviral therapy, includes a mixture of at least three antiviral medications in the standard ART protocol (WHO, 2015). Successful antiretroviral therapy (ART) frequently manages the replication of HIV in individuals who are infected and boosts the CD4 cell count, thereby extending the period of asymptomatic infection, delaying the advancement of the illness, and aiding in the decrease of transmission risk (Bhatti et al., 2016).

Since the introduction of powerful Combination Antiretroviral Therapy (cART) in 1996, the quality of ART for HIV infection has steadily increased. Due to ART, there has been a substantial decrease in HIV-related illness and death, turning HIV into a treatable long-term condition that allows people living with HIV to have a similar life expectancy to those without HIV (Samji et al., 2013; Lohse and Obel, 2016). The main objectives of starting treatment as per the DHHS guidelines are ensuring sustained and effective control of plasma HIV-1 RNA levels, restoring and maintaining immune function, reducing HIV-related illnesses, enhancing quality of life, extending survival time, and preventing transmission of the virus (DHHS, 2019; NASCOP, 2018).

The HAART treatment involves taking a mixture of three or more potent antiretroviral drugs, such as NRTIs, NNRTIs, and PIs. Efficient HAART controls viral replication, enhances immune function in people with HIV, and reduces drug resistance, leading to a significant improvement in the prognosis of HIV disease progression to AIDS (Hileman and Funderburg, 2017). Suggested first treatment options consist of 2 NRTIs (abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine) coupled with a third single or boosted medication. This third drug choice should be an integrase strand transfer inhibitor (dolutegravir, elvitegravir, or raltegravir), a NNRTI (efavirenz or rilpivirine), or a boosted PI (darunavir or atazanavir). Other treatment options exist (Gunthard et al., 2014).

The primary treatment for HIV, known as HAART, involves using a combination of various drugs that target different aspects of HIV replication. This approach helps prevent the virus from developing resistance to a single drug by utilizing multiple mechanisms to inhibit its multiplication. Multiple medications can be combined into one formulation to increase patient adherence to their prescribed drugs (Eggleton and Nagalli, 2020). The various drugs in combination ART have distinct modes of action, which collectively hinder HIV replication to prevent drug resistance. This helps to maintain low levels of viral load and reduce the chances of a more advanced mutation (Smyth et al., 2012). If a mutation that provides immunity to one drug emerges, the remaining drugs will still inhibit the growth of that mutation. With rare instances, no individual antiretroviral medication has proven effective in controlling an HIV infection over a prolonged period; multiple antiretroviral medications must be used together to achieve lasting results. Therefore, the standard treatment involves using a combination of various antiretroviral drugs (DHHS, 2019). Pharmaceutical companies have worked together in recent years to combine these intricate regimens into one-pill fixed-dose combinations (AIDS info). This significantly enhances the convenience of their intake, leading to better drug compliance and adherence, according to Bangalore et al. (2007).

2.8 Classification of Antiretroviral Drugs

There are six classes of anti-HIV drugs based on their therapeutic mechanisms and categories and over twenty antiretroviral drugs have been licensed for therapeutic use globally **(**Da –Yong et al., 2017). These antiretroviral (ARV) drugs work by inhibiting different phases of the retrovirus life-cycle and thus the basis of their classification (DHHS 2019). The following are the classes of the antiretroviral drugs:

NRTIs competitively bind to reverse transcriptase and induce early termination of DNA chain (Joseph et al., 2012; Kakuda, 2000; Saag et al., 2018;79). Some examples are: Abacavir (ABC), Didanosine (ddi), Lamivudine (3TC), Stavudine (d4T), Tenofovir, and Zidovudine (ZDV) (Kemnic & Gulick, 2024; Eggleton & Nagalli, 2023).

NNRTIs stand for non-nucleoside reverse transcriptase inhibitors. NNRTIs attach to HIV reverse transcriptase, leading to a modification in its structural shape which prevents nucleoside attachment and hinders DNA replication. This method prevents the creation of viral DNA from viral RNA (Kemnic & Gulick, 2024). Some examples are Delavirdine, Efavirenz (EFV), Nevirapine (NVP), and Rilpivirine. (Kemnic & Gulick, 2024; Eggleton & Nagalli, 2023).

Protease inhibitors (Pis) ((Kemnic & Gulick, 2024; Lennox et al., 2014). The Pis actively block the proteolytic cleavage of the gag/pol polyproteins in cells infected with HIV. The use of these agents leads to the creation of immature, noninfectious particles. Some examples are: Atazanavir, Darunavir, Indinavir (Kemnic & Gulick, 2024; Eggleton & Nagalli, 2023).

Integrase strand transfer inhibitors (INSTIs) were mentioned by Schafer and Squires in 2010, as well as Hazuda et al. in 2000. Stop the integration of viral DNA into the chromosome of the host cell. Some examples are Dolutegravir, Elvitegravir, and Raltegravir (Kemnic & Gulick, 2024; Eggleton & Nagalli, 2023).

Fusion inhibitors (Fis). Attach to the envelope glycoprotein gp41 and block viruses from attaching to the CD4 T-cells. Examples include: Enfuvirtide (Kemnic & Gulick, 2024; Eggleton & Nagalli, 2023).

Antagonists of the chemokine receptor CCR5 were studied by Dorr et al. in 2005. CCR5 inhibitors specifically and temporarily block the interaction between CD4 cells and the gp120 protein on the cell surface, preventing entry into the CD4 T-cells. Some instances are: Maraviroc (Kemnic & Gulick, 2024; Eggleton & Nagalli, 2023).

2.9 WHO Guidelines on Use of Antiretroviral Therapy

The initial release of the WHO ART guidelines was in 2002, and they have since evolved over time with the growing evidence supporting the early use of ART in HIV infection (Victoria et al., 2014). WHO released ARV guidelines in 2013. This advice was formed using medium-quality information from three controlled trials (Emery et al., 2008; Cohen et al., 2011; Grant et al., 2011). Information from Three randomized controlled trials showed that starting ART when CD4 count is at 500 cells/mm3 lowered the risk of developing AIDS and/or death, TB infection, non-AIDS-related illnesses, and improved immune recovery compared to delaying ART initiation at CD4 cell count of 350 cells/mm3 or lower. According to this information, in 2013 WHO advised starting ARV treatment for all HIV infected adults with a CD4 count at or below 500 cells/mm3, regardless of WHO clinical stage. This suggestion prioritized individuals with severe HIV illness or a CD4 cell count of 350 cells/mm3 or lower (WHO, 2013). Additionally, a randomized controlled study indicated that starting ART earlier can significantly reduce the likelihood of transmitting HIV to uninfected sexual partners (Cohen et al., 2011).

In 2015, WHO changed the traditional recommendation of waiting for HIV to progress to AIDS before starting treatment, and advised initiating ART for all HIV patients regardless of CD4 count or clinical stage (WHO, 2016). Priority for starting ART was given to individuals with advanced disease stage or a low CD4 cell count. In most cases, ART should begin within a week of being diagnosed with HIV or immediately on the day of diagnosis for those prepared to start treatment (WHO, 2017). This strategy is commonly referred to as the "Universal Test and Treat" (UTT) strategy. Accessible ART for HIV-infected individuals and expanding prevention methods to HIV-negative individuals could prevent 21 million AIDS-related deaths and 28 million new infections by 2030 (Levi et al., 2015).

Currently, the WHO has published updated guidelines on use of antiretroviral therapy (2021 Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach) which is an updated of the guidelines published in 2016 (WHO, 2021). The guidelines recommend initiating ART promptly after diagnosis, preferably within seven days. Advocating for ART for every individual with HIV, irrespective of clinical signs or CD4 cell levels. Utilizing preferred initial treatment regimens that rely on dolutegravir (DTG). Providing pre-exposure prophylaxis (PrEP) as an extra prevention option for individuals at high risk of contracting HIV. Providing prompt ART commencement to individuals diagnosed with HIV after confirmation and clinical evaluation. Prioritizing clinical evaluation and the start of treatment for individuals with advanced HIV disease. Recognizing and tackling structural obstacles that may postpone access to ART.
The WHO additionally advises nations to modify and apply these suggestions according to their specific epidemiological contexts (WHO, 2021).

Multiple studies suggest that starting ART during acute HIV infection may lead to lasting viral load control after stopping treatment, albeit rarely (Saez – Cirian et al., 2013; Persaud et al., 2013). Novel, powerful medications with lower toxicity and good tolerability make it easier to start and continue treatment early in life (34). In 2015, two research projects, START (Lundgren et al., 2015) and TEMPRANO (Danel et al., 2015), showed that starting ART immediately after diagnosis led to longer patient life compared to delaying until CD4 cell levels decrease.

2.9 Kenya ART Guidelines

The objective of ART is to inhibit viral replication in order to lower the patient's viral load to undetectable levels. The 2018 guidelines in Kenya for using antiretroviral drugs suggest that everyone with confirmed HIV should be considered for ART initiation, regardless of various factors, as long as they are willing and able to follow treatment advice (NASCOP, 2018). These factors are CD4 count/percentage, WHO clinical stage, age, pregnancy or breastfeeding status, co-infection status, risk group, or any other criteria, be considered for ART initiation on condition that the individual is willing and prepared to take ART and comply with follow-up advice (NASCOP, 2018). Antiretroviral treatment should begin in every individual diagnosed with HIV, ideally within a 2-week period after confirming their HIV status. The preferred first-line ART for HIV patients 15 years and older who are women and adolescent girls of childbearing age is TDF + 3TC + DTG (or TDF + 3TC + EFV). The guidelines also state that if a patient's Viral Load is ≥ 1,000 copies/ml after at least 6 months of taking antiretrovirals, treatment failure is assumed. However, treatment failure is confirmed when VL is still ≥ 1,000 copies/ml after investigating and dealing with possible reasons like not following the medication schedule (NASCOP, 2018).

2.10 Antiretroviral Therapy (ART) Regimens

Typically, treatment-naive patients are prescribed a starting ARV regimen that consists of two NRTIs, such as abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), along with a medication from either an INSTI, an NNRTI, or a boosted PI. In the majority of individuals living with HIV, this first treatment strategy has resulted in the inhibition of HIV replication and enhancement in CD4 count (Moore and Bartlett, 2011; Gill et al., 2010; Lee et al., 2014). The 2019 WHO updated recommendations on first- and second-line antiretroviral regimens are as follows (WHO, 2019).

2.10.1 First-line ART regimens

1. The suggested first-line regimen for people living with HIV who are starting antiretroviral therapy (ART) is Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone.
2. For HIV infected adults and adolescents who are initiating ART, low dose Efavirenz (EFV 400 mg) together with an NRTI backbone is proposed as the alternative first-line regimen
3. For infants and children for whom authorized DTG dosing is not available, a Raltegravir (RAL)-based regimen may be suggested as the substitute first-line regimen
4. For newborns, a RAL-based regimen may be prescribed as the ideal first-line regimen.

2.10.2 Second-line ART regimens

1. For PLWHIV for whom non-DTG-based regimens are ineffective, DTG along with an optimized NRTI backbone may be suggested as a favored second-line regimen
2. For PLWHIV who are not responding to DTG-based regimens, boosted protease inhibitors together with an optimized NRTI backbone are proposed as a preferable second-line regimen.

2.11 Effect of Long Term ART Toxicity

Sooner initiation of ART increases probability of ARV adverse effects. For example, it was stated that cumulative exposure to some drugs of the Nucleoside Reverse Transcriptase Inhibitor (NRTIs) and Protease Inhibitors (PI) drug classes might be associated with increased incidence of Cardiovascular Diseases -CVD (Seyed, 2016; Friis-Møller et al., 2007; Worm et al., 2010). Also, continuous exposure to ART was associated with significantly greater loss of bone density compared with interruption or deferral of therapy (Seyed, 2016; El-Sadr et al., 2006). Also, there may be unidentified complications linked to cumulative use of ARV drugs for many decades.

2.11.1 Effect of Early ART Initiation on Quality of Life

ART frequently causes an improvement in the quality of life for symptomatic patients. On the other hand, some side effects of ART may reduce quality of life for some persons, especially those asymptomatic at early therapy. For example, PIs may induce nausea or efavirenz may have disturbing neuropsychiatric side effects. These side effects can be very infuriating in an asymptomatic patient. Thereby, in spite of strong evidences on ART long term benefits, some people find that the inconvenience of taking medication every day outweighs the overall benefits of early ART and may select to defer treatment (Seyed, 2016).

2.11.2 ART for Patients with a History of an AIDS-Defining Illness or CD4 Count <350 Cells/mm3

PLWH with diseases, CD4 counts non-AIDS <200 cells/mm morbidities and patients with CD4 counts <200 cells/mm 3 3 are death. at greater Randomized risk of opportunistic controlled trials in and/or a history of an AIDS-defining condition greatly support the positive impact of ART on improved survival and delay in disease progression in PLWH (Seyed, 2016; Hammer et al., 1997; Zolopa et al., 2009). In addition, comparative data from several observational cohort researches between earlier ART (i.e. initiated at CD4 count >200 cells/mm 3) with later treatment (i.e. initiated at CD4 count <200 cells/mm 3) showed robust evidence for these results (Seyed, 2016; Sterne et al., 2009; Baker et al., 2008). In patients with CD4 counts of 200 cells/mm 3 to 350 cells/mm3 those who delayed ART had a higher mortality rate compared to those who started therapy (Seyed, 2016; Severe et al., 2010). Together, these researches support the initiation of ART in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm3.

2.11.3 ART During Acute HIV Infection

Early initiation of ART decreases the severity of immune system destruction, lessens during both after which the short-term anti-HIV and the infection during antibodies long-term which are effects undetectable of anti-HIV while HIV antibodies are HIV infection, RNA detectable) or and reduces the risk of HIV transmission. The DHHS Guidelines recommend ART to PLWH with early HIV infection. In this guideline, early HIV infection consisted of acute HIV infection (the phase of HIV disease immediately after infection p24 antigen are present) and recent infection (considered the phase up to 6 months (Department of Health and Human Services, 2014).

Recommendation of International AIDS Society in this regard is the same (Günthard et al., 2014). Its recommendation is based on studies suggesting reduction of proviral DNA and plasma viral load, lower viral set point, robust immune reconstitution, and CD4 cell count increases greater than 900/µL (Günthard et al., 2014). But none of the above benefits lasted for more than 24 months after treatment discontinuation. So discontinuation of ART after any duration of treatment is not recommended except in research situations (Günthard et al., 2014).

2.12 Routine Assessment and Follow-Up of The Newly Diagnosed HIV-Positive Individual

2.12.1 First Assessment

The first assessment of a newly diagnosed individual provides the opportunity to discuss HIV, perform a thorough medical, psychological and social review and to request the investigations that will provide the baseline for future monitoring and intervention. At this visit the foundations for high-quality care are laid; the clinician has the opportunity to ascertain the patient's knowledge and evaluate their need for further information and support. In the UK, national guidelines recommend that all newly diagnosed patients are reviewed by an HIV clinician within 2 weeks, sooner if they have symptoms or other acute needs (Alder et al., 2012).

2.12.2 History

A detailed medical, social and psychological history should be performed at baseline. A thorough review of symptoms may guide targeted physical examination and additional investigations. Additional assessment tools may be useful as indicated by the history, for example screening questionnaires for depression/ anxiety (Alder et al., 2012).

2.12.3 Examination

A full examination of all body systems is recommended; particular attention should be paid to thorough palpation for lymphadenopathy, careful skin and mucous membrane examination. All patients with a CD4 count less than 50 cells/μL should have dilated fundoscopy to exclude retinal pathology, particularly cytomegalovirus (CMV) retinitis. This should ideally be performed by an experienced ophthalmologist. The following baseline measurements should be documented; weight, height and body mass index (BMI), blood pressure, waist circumference and/or waist–hip ratio (Alder et al., 2012).

2.12.4 Investigations

All newly diagnosed HIV-positive individuals should undergo confirmatory laboratory diagnosis of HIV infection, including discrimination between HIV-1 and HIV-2. Avidity assays may be available, depending on local surveillance, to determine whether infection is recent (within 3–6 months) or chronic (more than 6 months). These have been validated for epidemiological purposes; communication of results to patients must be cautious, emphasizing the degree of uncertainty. Routine baseline investigations, as recommended in the BHIVA Routine Investigation and Monitoring Guidelines (2011), are summarized in Table 6.1. Mental health disorders are common in HIV-infected individuals and confirmed mental health diagnoses are, themselves, a risk factor for HIV acquisition. Many aspects of living with HIV can impact on mental health. All patients should undergo a mental health assessment by a clinician and a specialist health advisor, with a low threshold for referral to counselling, psychology or psychiatry services as indicated. HIV is associated with neurocognitive impairment, although, in most cases, it is asymptomatic or mild. Controversy remains regarding prevalence, aetiology and prognosis; there is a lack of consensus regarding value of screening and the most appropriate screening tool (Alder et al., 2012).

2.13 Interventions and Discussion

2.13.1 Contact tracing and partner notification

Thorough contact tracing and partner notification is essential; careful documentation of this, and eventual outcomes, must be performed. A patient may wish to delay disclosure to partners; some delay may be acceptable if there is no urgency (i.e. no ongoing risk behaviour). Attempts to encourage and support disclosure and testing of contacts should be made regularly; if refusal continues then additional action may be required. Some newly diagnosed individuals will have a known HIV-positive partner; for others, partner testing will be required. Support around disclosure and testing of their partner should be available. Testing of children is a sensitive area and specialist input should be sought (Alder et al., 2012)

2.13.2 Safe sex and transmission

There should be a clearly documented discussion of the following issues; safer sex, importance of STI screening, indications for post-exposure prophylaxis (PEP) and when/how to access, transmission risks including impact of concurrent STI, the issue of 'reckless transmission' and litigation.

2.13.3 Prognosis and general health

Newly diagnosed individuals should be reassured regarding the impact of cART on health and life expectancy; most individuals can be advised to plan for a normal life expectancy. General health measures should be emphasized, such as exercise, nutrition and smoking cessation, particularly as HIV is associated with an increased risk of many co-morbidities. Patients travelling abroad should be counselled about simple precautions such as infection prophylaxis and water safety where appropriate (Alder et al., 2012).

2.13.4 Social and occupational considerations

Newly diagnosed individuals should be given advice, including onward referral to other agencies if required, regarding support groups, employment rights and access to benefits; in the UK, HIV. Patients whose occupation may be affected by their HIV status should be provided with the relevant information and, with consent, referred to their occupational health service (Alder et al., 2012).

2.13.5 Immunization

Respiratory illnesses are more common in HIV-positive individuals irrespective of CD4 count. Influenza vaccination should be provided annually. Immunization with the 23 valent pneumococcal vaccine is recommended in all HIV-infected adults. As outlined in Table 6.1, individuals who are non-immune to hepatitis B, measles, rubella or varicella should be offered vaccination; those non-immune to hepatitis A should be vaccinated as indicated (e.g. hepatitis B/C coinfection, men who have sex with men and drug users). Varicella vaccine responses are best at CD4 counts above 400 cells/μL but consider vaccination if over 200 cells/μL. Combined measles/mumps/ rubella (MMR) vaccine should be offered to those non-immune to measles and/or women of child-bearing age who with no rubella immunity, ideally at CD4 >200 cells/μL. Hepatitis B vaccine can be commenced at any CD4; optimal antibody response may not be achieved at low CD4 and repeat vaccination may be required (Alder et al., 2012)

2.14 Adverse Drug Reactions Due to Antiretroviral Therapy

Thankfully, the advent and widespread use of HAART has drastically modified the natural evolution of HIV infection. As a result, people living with HIV/AIDS (PLWHA) can now live longer, have better prognosis and improved quality of life than in the past (UNAIDS, 2016). In addition, the implementation of the "test and treat" scheme will result in a drastic increase in the number of individuals accessing ART in the immediate future. (Maartens et al., 2014). These medications, however, have been linked to severe ADRs which may result in drug resistance and a switch of ART regimen (Tenore, 2016; Shet et al., 2014; Vo et al., 2008) and appearance of new comorbid conditions that may result in reduced adherence and thus resulting in virological failure (WHO, 2016; Domingo et al., 2011,). It has been illustrated that the timing, form and duration of ADRs are influenced by type of ART regimen used (Masenyetse et al., 2015; Orrel, 2011). the most frequent causes of treatment failure are lack of adherence and insufficient adherence because the use of drugs in insufficient or inconsistent doses speeds up the process of selection of virus strains that are drug resistant, putting the effectiveness of ART in jeopardy at the personal level and resulting in the spread of resistant viruses on a larger scale (Mlontaner et al., 2014; Brenchley et al., 2004). The development of undesirable effects from ART use has been demonstrated in research studies to be a contributing factor for lack of adherence (Ibrahim et al., 2014; Achappa et al., 2013; Daniel and Veiga 2013; Reda and Biadgilins 2012).

ART-related adverse effects can occur immediately after drug administration, a few days or weeks after or months after treatment. Harmful drug effcets can range from mild to severe to fatal and they can be drug specific or non-specific according to the category of drugs in question (WHO, 2010).

Drug-induced bone-marrow suppression (anaemia, neutropenia and, more rarely, thrombocytopenia) are more frequently caused by AZT. The main side effects of ART can be classified into the following; Gastrointestinal (Tadese et al., 2014; Nagpa et al., 2010), Central nervous system, (Nagpa et al., 2010), Hematological (Tadese et al., 2014), Psychological (Tadese et al., 2014), Metabolic (Tadese et al., 2014; Nagpa et al., 2010;) Musculoskeletal (Nagpa et al., 2010) and Miscellaneous types: Hypersensitive reactions, oral ulcerations, fever, and irregular menstrual cycles (Nagpa et al., 2010).

2.14.1 Haematologic Toxicity

Some of the antiretroviral drugs used for management of HIV frequently cause haematologic toxicity (Balakrishnan et al., 2010). The usual ART-related haematological abnormalities include the pancytopenias (reduction in all blood cell counts) and CD4 T cell loss (Dikshit et al., 2009). A well-known reverse transcriptase drug, AZT has been linked to the development of cytopenias in HIV infected patients (Hawkins, 2010). Myelosuppression accompanied with presence of macrocytes has been commonly found in AZT treated HIV patients as well as several other chemotherapeutic agents (Gunthard et al, 2014). Findings from a study of haematologic abnormalities among children pre and post ART reported that 85.7% of those who developed anaemia after treatment with ART received AZT-based regimen (Geletaw et al., 2017). Utilization of AZT, a component of Zidolam has been linked to development of Haematologic toxicity, neutropenia and anemia especially in patients at advanced stages of HIV-1 disease (Viiv Healthcare, 2010; AIDinfo, 2009; Montesori et al., 2004). Zidolam results in emergence of anaemia from 2 – 4 weeks of drug taking (NAM, 2010). A study conducted to investigate haematotoxicity effects of zidolam in albino rats, demonstrated that Zidolam produced leucopenia and anaemia, neccessitating the inclusion of pharmaceuticals that could improve the hematological parameters in the medications of patients undergoing ART (Osonuga et al., 2011). Risk factors for AZT-related haematologic toxicities are related to pre-treatment bone marrow reserve and to dose and length of therapy. In particular, progressed HIV disease, anaemia- related opportunistic infections such as Mycobacterium Tuberculosis and Mycobacterium Avium Complex (MAC), injection drug use, higher dose AZT, preceeding neutropaenia or anaemia concurrent use of myelosuppressants such as cotrimoxazole, anti–tuberculosis drugs or drugs that cause haemolytic anaemia such as ribavirin are the potential risk factors (71). Findings of a previous study reported that Hematological adverse reactions represented 3.8% of all adverse drug reactions of which anemia (haemoglobin less than 7g/dl) was the most frequent and most seriouse; all of which were linked to use of AZT-containing regimens (Luma et al., 2012). Zidovudine is a much less administered drug for PLWHA in this cART era due to its haematological adverse effects and the availability of alternative choices. Anaemia caused by myelosuppression is far less common with the modern cART choices (Gunthard et al., 2014).

2.14.2 Haematological Abnormalities In HIV Infected Patients

Haematological abnormalities are typical complicacies of HIV infection and they escalate as the disease progresses. The prevailing haematological abnormalities are diverse in both ART-exposed and ART non- exposed individuals (Dikshit et al., 2009; Muluneh et al., 2009; Gange et al., 2003). HIV linked haematological abnormalities appear to be dependent on the degree of virus reproduction, since these abnormalities are more grievous in end-stage AIDS patients with high numbers of viruses in the bloodstream. All cell lineages in the marrow are affected by these abnormalities which are demonstrated by impaired haemopoiesis, cytopenias and coagulopathy [Parinitha and Kulkarni, 2012]. Ineffective haematopoiesis can be caused by HIV infection, either directly by suppressing bone marrow progenitor cells or indirectly through increased release of HIV –induced inflammation cytokines leading to diminished hematopoiesis. Likewise, deficiency of nutrients, deleterious effects of drugs and diseases that infiltrate the bone marrow as a result of infectious or neoplasms can also cause ineffective haematopoiesis (Vishnu and Aboulafia, 2015). Leucocytes and platelets, essential elements of the immune system that play a role in containing pathogenic microorganisms, frequently show abnormalities in people infected with HIV [Cao et al., 2022; Bisetegn & Ebrahim, 2021). The WHO supports the use of total lymphocyte counts as a substitute indicator for long-term CD4+ T cell count, particularly in low-income countries (WHO, 2023).

HIV infected patients have a lowered quality of life as a result of the severe symptoms caused by the diverse haematological abnormalities, which may be a hindrance to effective treatment of acute HIV infection, opportunistic infections or associated neoplasm. Remedying haematological abnormalities can reduce the complicacies and enhance the quality of life (Attiliv, 2008). The most prevalent haematological abnormalities seen in HIV infected patients are the cytopenias, among others (Redig and Berliner, 2013). In all situations, a precise diagnosis of the causation, intensity and mechanism of cytopenia should be investigated, since its remedy may necessitate the use of a particular intervention besides use of ARV drugs. Subject to the choice of combination ART utilized, ARV drugs could have a favorable or negative impact on the haematological markers (Moore et al., 1998). Hematological disorders are linked to higher morbidity and mortality rates in patients with HIV, impacting their quality of life (Kathuria et al., 2016). Prior research has shown different prevalence rates of anemia, thrombocytopenia, and leukopenia in individuals infected with HIV. (Haile et al., 2023; Bisetegn et al 2021; Gunda et al., 2017; Bhardwaj et al., 2020; Getawa et al., 2020).

2.14.3 Cytopenias

Cytopenias in HIV infected patients are the result of defective haematopoietic system while increasing immunological malfunction is caused by immune system attack by HIV (Durandt et al., 2019). Cytopenias are the most prevalent haematological aberrations of HIV infection and may affect any of the major blood cell lines leading to low levels of red blood cells, white cell and platelets. Cytopenias are caused by a variety of factors, including, HIV infection itself, adverse effects of drugs, co-infection with HBV and HCV, opportunistic infections among others. Excessive cell destruction/cell loss in the peripheral circulation and defective blood cell production from the bone marrow are the two categories of these cytopenia's physiopathology (Durandt et al., 2019; Opie, 2012; Koka and Reddy, 2004). As CD4 levels decreases and HIV infection progresses cytopenias become more common and severe. Cytopenias can impede ART thus influencing the aftereffects of HAART resulting in increased morbidness, deaths, and a decreased quality of life (Kathuria et al., 2016; Vishnu and Aboulafia, 2015; Pasha, 2004). Predisposing factors for cytopenias in HIV-infected patients are lower $CD4^+$ cells, high number of viral particles in blood, late stages of AIDS, and ARV drugs adverse effects (Kyeyune et al, 2014). The extent of any cytopenia was 40% in adult HIV-infected individuals undergoing highly active antiretroviral therapy, and the prevalence rose as the CD4 count declined (Gebreweld et al., 2020). Anaemia has been associated with advancement in HIV disease, high death rate, pancytopenia linked to hospitalization, while neutropenia is linked with secondary infections caused by bacterial and fungal pathogens or HIV drugs (Tamir et al., 2018; Dai et al., 2016; Santiago – Rodriquez et al., 2014; Kuritzkes, 2000; Jacobson et al., 1997). It has been shown that HAART leads to significant decrease in AIDS-associated deaths and ameliorates cytopenia (Tamir et al., 2018; Woldeamanuel and Wondimu 2018; O'Bryan et al., 2015; Johansen et al., 2011; Berhane et al., 2004; Moore and Forney, 2002).

2.14.4 Anaemia

The causes of anemia among HIV-infected patients are multifactorial which include the direct and indirect impact on the survival and functioning of bone marrow hematopoietic stem/progenitor cells (HSPCs) (Marchionatti & Parisi, 2021; Durandt et al., 2019). In addition, the drugs used for ART, inflammatory mediators released during HIV infection and coinfections or opportunistic infections could also affect the proliferation and differentiation of HSPCs during hematopoiesis (Marchionatti & Parisi, 2021; Durandt et al., 2019;). The principal factors are infiltration of the bone marrow by neoplasm or infection, myelo-suppressive medications such as Zidovidine, HIV infection itself, decreased production of endogenous erythropoietin, hemolytic anemia that may result from RBC auto-antibodies or may also develop as a consequence of the use of various medications (Mata-Marín et al., 2010; Volberding et al., 2004).

Cytokine imbalance can affect hematopoietic progenitor cells in different ways. Increased IL-6 induces augmented production of hepcidin, an important regulator of iron homeostasis. The increase of hepcidin is responsible for the retention of iron inside the macrophages and enterocytes, which leads to a decrease in serum iron concentration and, consequently, a decrease in hemoglobin production (Vishnu & Aboulafia, 2015; Redig & Berliner, 2013). In fact, severe anemia in PLWHA was related to decreased serum iron concentration (Obirikorang et al., 2016). In addition, IL-1β and TNF-α cytokines inhibit the production of erythropoietin, interfering with the proliferation of erythrocyte precursor cells (Parinitha & Kulkarni, 2012).

Hepcidin causes degradation of ferroportin, membrane protein transporting the iron. Ferroportin is expressed mainly in duodenal enterocytes and on macrophages. Increased hepcidin levels inhibit the absorption of the alimentary iron from gastrointestinal tract and its utilization from old erythrocytes. It results in decreased serum iron concentration and its availability for hemopoesis. Thus, hepcidin is a major regulatory iron hormone. Altered hepcidin production and iron metabolism play an important role in the pathogenesis of many acute and chronic infections, as the microorganisms use the iron acquired from the host for their own life processes (Drakesmith & Prentice, 2012).

Anemia has been identified as the most frequently occurring cytopenia in HIV infected patients (Tamir et al., 2019; Assefa et al., 2015; Kyeyune et al., 2014) and its prevalence varies significantly among studies ranging from 1.3% to 95% (Belperio & Rhew, 2004). Even in the antiretroviral therapy (ART) era, anemia has been described as the leading cytopenia reported in approximately 50%, followed by leukopenia and thrombocytopenia (Kyeyune et al., 2014). Type of ART regimen, occurrence of opportunistic infections, level of education, length of taking ART, monthly income, previous treatment with antituberculosis drugs, late-stage AIDS, gender, white blood cell levels below < 4,000 cells/μL, CD4+ cell levels below < 200 cells/μL, and platelets less than < 200,000 cells/μL are the anaemia associated factors among others (Tadesse et al., 2014; Adeba, 2014; Gedefaw et al., 2013). Several studies have reported that the incidence of anemia in HIV infected seropositive females is higher in females when compared to males (Thulasi et al., 2016; Sullivan et al., 1998)

The typical haematological aberration seen in HIV infected patients is anemia, with a prevalence of between 1.3% to 95% where normocytic normochromic anemia is the prevailing type succeeded by microcytic anemia (Subhash et al., 2020; Panwar et al., 2016; Pande et al 2011; Akinbami, 2010; Dikshit 2009; Behler et al., 2005; Belperio and Rhew 2004; Patwardhan et al., 2002). Study findings in HIV patients not exposed to bone marrow suppressing drug reported that 8% of non-symptomatic HIV-seropositive patients, 20% of those with symptoms and in intermediate-stage HIV disease, and 71% having Centers for Disease Control (CDC)-defined AIDS had anaemia (Zon and Groopman, 1988). Chronic illness, deficiency of nutrients, toxic effects of drugs and opportunistic infections, all have a role in the advancement of anemia in HIV patients. Anaemia becomes more prevalence and severe as HIV disease advances (Belperio and Rhew 2004; Volberding 2002). HIV infection directly causes persistent activation of the immune system and inflammation. In this inflammatory setting, release of dietary iron from enterocyte is inhibited; on the other hand, circulating iron is redistributed into cellular storage sites such as macrophages (Quiros – Roldan et al., 2017). Hepcidin plays a crucial role in these steps, by restricting the amount of iron available for hematopoiesis (Vyoral and Petrk, 2005). There is paucity of information on hepcidin levels in HIV positive patients [Gomes and Gomes 2016; Kerkhoff et al., 2016).

As CD4 cell levels fall, severity of anemia worsens (Thulasi et al., 2016; Dikshit et al., 2009;) HIV/AIDS late stages advances as HIV disease progresses (Alamdo et al., 2015). Furthermore, regardless of the CD4 T cell levels and VL, severe anemia alone is also a favorable circumstance for progression of HIV/AIDS (Takuva et al., 2013). Additionally, anemia affects the natural course of HIV/AIDS disease (Masaisa et al., 2011) thus lowering the rate of survival. This data has been proven in several previous studies conducted in third world (Meidani et al., 2012; Subbaraman et al, 2009). Previous studies conducted in sub-Saharan Africa region demonstrated that anemia prevalence among PLWHA receiving ART varied from 20.9% to 70.1% (Alem et al., 2013, Denue et al., 2013; Assefa et al., 2015; Enawgaw et al., 2015; Melese et al., 2017). However, recently Thulasi et al (2016) and Shubahsh et al, (2020) have reported a 74% anaemia prevalence in ARV treated HIV patients and that anaemia severity and incidence among ART – untreated HIV patients are a bit higher. Additionally, earlier research conducted throughout the world have likewise revealed varying proportions of anaemia prevalence in ART –naïve HIV patients with India reporting 22%, Ethiopia 35%, Uganda 47.8%. (Kyeyune et al., 2014; Ferede and Wondimeneh, 2013; Nascimento et al., 2012). A study conducted in rural Tanzania by Johannessen et al (2011) reported reported a 77.4% prevalence of anemia among ART-untreated HIV-positive adults while Daka et al (2013) published 86.5% anemia prevalence in ART-unexposed HIV infected Ethiopian patients. Studies conducted in Benin City, Rwanda, and Ethiopia found lower anemia prevalence in HAART treated patients as opposed to patients not receiving HAART (Fekene et al., 2018; Masaisa et al., 2011; Omaregie et al., 2009).

Type of ART regimen, occurrence of opportunistic infections, level of education, length of taking ART, monthly income, previous treatment with antituberculosis drugs, late-stage AIDS, gender, white blood cell levels below < 4,000 cells/μL, CD4+ cell levels below < 200 cells/μL, and platelets less than < 200,000 cells/μL are the anaemia associated factors among others (Tadese et al., 2014; Wolde et al., 2014; Gedefaw et al., 2013). Anaemia severity is strongly linked to mortality in addition to higher levels of inflammatory markers such as IL12 (Dhurve and Dhurve, 2013; Dunenport et al., 2012).

2.14.5 Thrombocytopenia

2.14.5.1 Etiology of Thrombocytopenia

Common causes of thrombocytopenia include Primary immune thrombocytopenia (primary ITP). An autoimmune condition where antibodies are produced against platelets resulting in platelet destruction. Drug-induced immune thrombocytopenia: this can be due to Heparin-induced thrombocytopenia (HIT) - in this condition, anti-platelet antibodies activate platelets resulting in thrombosis (both arterial and venous), Quinine, Sulfonamides, ampicillin, vancomycin, piperacillin, Acetaminophen, ibuprofen, naproxen, Cimetidine, Glycoprotein IIb/IIIa inhibitors, Other over the counter remedies, supplements, foods like African bean, sesame seeds, walnuts) and beverages (herbal teas and cranberry juice). Drug-induced non-immune thrombocytopenia is another cause of thrombocytopenia. Drugs like valproic acid, daptomycin, linezolid cause thrombocytopenia by dose-dependent suppression of platelet production. Infections such as Viral: HIV, hepatitis C, Ebstein-Barr virus, parvovirus, mumps, varicella, rubella, Zika viral infections can cause thrombocytopenia, Sepsis causes bone marrow suppression, Helicobacter pylori, Leptospirosis, brucellosis, anaplasmosis, and other tick-borne infections are associated with thrombocytopenia Malaria, babesiosis intracellular parasite infections are associated with thrombocytopenia and hemolytic anemia, Hypersplenism due to chronic liver disease, Chronic alcohol abuse, Nutrient deficiencies (folate, vitamin B12, copper). Autoimmune disorders like systemic lupus erythematosus, rheumatoid arthritis associated with secondary ITP. Pregnancy; Mild thrombocytopenia presents in gestational thrombocytopenia; moderate-severe thrombocytopenia can occur in preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome (Karimi et al., 2016; Kam and Alexander, 2014; Achterberg et al., 2012; Ohmori et al., 2004; Scaradavou, 2002; Davis et al., 2001; Azuno et al., 1999; George et al 1998; Arnold et al., 1998; Lavy, 1964) Other causes include Myelodysplasia, Malignancy such as cancer with chronic DIC, cancer with marrow suppression (leukemia, lymphoma, solid tumors), Paroxysmal nocturnal hemoglobinuria (PNH), Thrombotic microangiopathy (TMA). Thrombotic thrombocytopenic purpura (TTP), a condition manifested by fever, renal failure, thrombocytopenia, microangiopathic hemolytic anemia with or without neurologic manifestations. A hemolytic uremic syndrome (HUS) caused by Shiga toxin-producing organism (E. coli and Shigella), seen in children, Drug-induced TMA: quinine, specific chemotherapy agents, Antiphospholipid antibody syndrome, Aplastic anemia, Inherited thrombocytopenia. Often seen in children, rare in adults. These include Von Willebrand disease type 2, Alport syndrome, Wiskott-Aldrich syndrome, Fanconi syndrome, Thrombocytopenia-absent radius syndrome, Bernard–Soulier syndrome, May-Hegglin anomaly (Clare et al.,1979)

2.14.6 Pathophysiology of thrombocytopenia

2.14.6.1 Decreased platelet production

Decreased platelet production can be as a result of Bone marrow failure presents in aplastic, anemia, PNH, Bone marrow suppression is a feature with exposure to certain drugs, such as valproic acid, daptomycin, certain chemotherapy agents, and irradiation, Chronic alcohol abuse, Inherited thrombocytopenia), Viral infection, Systemic conditions like nutrient deficiencies (folate, vitamin B12), sepsis, myelodysplastic syndrome impairs platelet production in the bone marrow - these conditions also associated with decreased production of other cell lines leading to anemia and leukopenia (Franchini, 2017; Vener et al., 2009).

Increased platelet destruction

In normal conditions, platelets get removed by monocytes/macrophages of the reticuloendothelial system. The life span of platelets is 8 to 10 days. In immune-mediated thrombocytopenia, anti-platelet autoantibodies bind to platelets and megakaryocytes, resulting in increased platelet destruction by the reticuloendothelial system and decreased platelet production. Anti-platelets antibodies are present in primary ITP, drug-induced ITP, lymphoproliferative disorders, and autoimmune conditions like SLE and in chronic infections like HEP C, HIV, and Helicobacter pylori. Non-immune mediated increased platelet destruction occurs in mechanical valve replacement patients, preeclampsia/HELLP syndrome, DIC, and thrombotic microangiopathy. In conditions like DIC and thrombotic microangiopathy, increased platelet consumption within thrombi takes place (Franchini et al., 2017; Kuwana M 2014; Stasi R 2012; Dowling et al., 2010; Mason et al 2007; Budman and Steinberg, 1977)

2.14.6.2 Dilutional thrombocytopenia

Dilutional thrombocytopenia presents in massive fluid resuscitation and massive blood transfusion (Lesli and Toy, 1991)

2.14.7 Redistribution of platelets

In normal individuals, one-third of platelet mass is in the spleen. In conditions that cause splenomegaly and increases spleen congestion (cirrhosis) results in increased platelet mass in spleen and a decrease in circulating platelets (Aster, 1966).

Thrombocytopenia is considered the first hematological manifestation of HIV infection. The presence of thrombocytopenia may change according to the CD4+ T lymphocyte count, the age, the presence of HCV/HBV coinfection, the presence of opportunistic infections and the ART treatment. Occurrence of thrombocytopenia is a predictor of morbidity and mortality in PLWHA, leading to an accelerated progression to AIDS (Taremwa et al., 2015; Vishnu & Aboulafia, 2015; Wondimeneh et al., 2014).

After anaemia, thrombocytopenia comes second in the order of most common complication of HIV infection with 3-40% of HIV infected patients presenting with thromcocytopenia and it can be seen at any phase of HIV infection. Chronic immune thrombocytopenic purpura has now been shown to be a characteristic of chronic HIV infection (Liebman, 2008). Occurrence of thrombocytopaenia does not depend on the advancement of HIV disease. Thrombocytopenia in HIV infected individuals is primarily caused by inefficient production and excessive platelet destruction which both occur simultaneously (Kuter, Phil and Gernsheimer, 2009). Destruction of platelets by antibodies, cross –reactive antibodies produced against viral proteins, especially gp120 and p-24 are the probable mechanisms that have been suggested to cause thrombocytopenia. Platelet destruction usually takes place in the early stages of HIV infection however are a bit more common in patients with advanced HIV disease (Mira et al., 2015) and the destruction is frequently immune-mediated (Fan et al., 2015; Mira et al., 2015; Taremwa et al., 2015; Kumar et al., 2010). Direct effects of viral infection of megakaryocytes is the other frequent cause of decreased production of platelets in HIV infected patients (Parnitha and Kulkarni, 2012). This results to morphological abnormalities of megakaryocytes in the bone marrow. Infiltration of the bone marrow by opportunistic infections or lymphomas and myelosuppressive effects of drug therapy also contribute to thrombocytopenia.

Previous studies have reported thrombocytopenia in HIV-infected patients; where a study from northern Ethiopia indicated that 4.1% and 9.0% of the study participants on HAART and HAART naïve respectively were thrombocytopenic (Enawgaw et al., 2014) while 8.3% of the Ugandan study subjects who were HAART naïve or on HAART were thrombocytopenic (Kyeyune et al., 2014), while a study conducted in 2010 indicated that 16.1% of ART-naive patients in a Nigerians were thrombocytopenic (Akinbami et al., 2010). A prevalence of 11.1% was reported by Fekene et al (2018) in Ethiopia in both HAART and HAART naïve HIV positive patients and a thrombocytopenia prevalence of 18.7% was reported by Tamir et al (2019) in ART- unexposed HIV positive patients in Dessie, Ethiopia. Thrombocytopenia prevalence is not linked to the level of immunosuppression and the HIV clinical stages (Fekene et al., 2018; Akinbami et al.,2010). However other research findings reported that patients with lower CD4+ levels or in late-stage HIV disease had more severe and prevalent thrombocytopenia (Gunda et al., 2017; Thulasi et al., 2016; Saha et al., 2015). According to Thulasi et al (2016) patients not on ART treatment have a slightly higher prevalence of thrombocytopenia as opposed to those receiving ART which is likely due to disease improvement after the start of HAART and the prevalence of thrombocytopenia is higher in patients with low CD4 cell levels. Fekene et al (2018) also indicated that patients receiving non-Zidovudine- based HAART regimen had a higher thrombocytopenia prevelence than those receiving Zidovudine-based HAART regimens.

2.14.8 Leucopenia and Neutropenia

Decreased activity of the bone marrow as a result of infiltrations, accelerated apoptosis and direct effects of HIV itself, impaired granulopoiesis, infectious agents, malignancies, and antibodies against granulocytes are all possible causes of leucopenia in HIV infected patients (Gunda et al., 2017, Donald W, 1998) and toxicity of the drugs used to treat HIV infection (Thulasi et al, 2016). Previous studies conducted in Africa region have reported varying prevalence of leucopenia in both ART –unexposed and ART exposed HIV infected individuals such as 24.3% in Uganda (Kyeyune et al., 2014], 23.6% in Tanzania (Gunda et al., 2017), 4.8% in Ethiopia [Addis, Yitayew and Tachebele, 2014), 26.2% in Gondar, Ethiopia (Enawgaw et al., 2014), 26.8% in Lagos, Nigeria

(Akinbami et al., 2010), 4.6% in Cameroon (Wankah et al., 2014) and 18.33% in India (Subhash et al., 2020).

The most frequent type of leucopenia is neutropenia occurring in 5–30% of HIV patients showing early symptoms of HIV infection and up to 70% of those with advanced AIDS stages (Vishnu and Aboulafia, 2015; Evans and Scadden 2000; Calenda and Chermann, 1999). HIV-related neutropenia, analogous to other cytopenias, is caused by a variety of factors including HIV infection itself, opportunistic infections, malignancies, autoimmune conditions, and drugs used to treat HIV drugs (especially AZT-containing regimens), medications for opportunistic infections, cotrimoxazole, and the like, which are toxic to the bone marrow (Leroi et al., 2017; Shi et al., 2014; Evans and Scadden 2000). Zidovudine (ZDV), a first-line ARV drugs endorsed since 2000, continues to be widely used in spite of the WHO 2013 recommendations advocating the use of tenofovir (TDF) in first-line to treat everyone (WHO, 2013).

Neutropenia in HIV patients has been reported in previous studies with a prevalence of 10.8% reported by Babadoko et al (2015) and Hoxie et al (2013). However, Dikshit et al (2009) did not find any cases of neutropenia in their study conducted on 200 HIV patients. Moreover, a significant relationship between CD4 counts and the total leucocyte count was not found (Enawgaw et al., 2014). It has been reported that neutropenia is more commonly present in HIV patients on first line ART, especially AZT-containing ART regimens, and those having lowered CD4+ cell levels (Dikshit et al., 2009). There is considerable variation geographically in the prevalence of neutropenia among HIV patients from different geographic regions. For instance, a worldwide study investigating the effects of cART on health-related outcomes, neutropenia prevalence among greater than 1500 HIV-infected patients was ≤5% among Indian and Peruvian patients and ≥15%

among Malawian, Zimbabwean, and South African, Haitian, and United States patients (Firnhaber et al., 2010). Reduction in neutropenia has been linked to the use of cART (Gunthard et al., 2014).

2.15 Immunologic Marker of HIV Infection

2.15.1 CD4 Cells

Chronic human immunodeficiency virus (HIV) infection causes progressive destruction of CD4+ T cells and profound immune suppression, increasing the risk for opportunistic infections (Saharia & Koup, 2013). As a target of HIV infection, CD4+ T cells, also known as The T helper (Th) cells play a critical role in the modulation of innate immunity and initiation of adaptive immunity by their production of cytokines and chemokines to orchestrate the full panoply of immune responses (Boucau et al., 2020; Porichis et al., 2018; Rashighi & Harris, 2017).

The T helper (Th) cells have been characterized into two subgroups i.e. Th1 and Th2 with differing pattern of cytokine profiles (Carlberg et al., 1997). Th1 pattern of cytokines are characterized by secretion of IL-2, IL-12 and IFN–γ. These cytokines are associated with a protective response. On the other hand, the Th2 specific cytokines i.e. IL-4, IL-5, IL-6, IL-10 and IL-13 are associated with disease progression and lead to the progression of HIV infection to AIDS (Soufian et al., 2012).

The World Health Organization (WHO) 2016 consolidated treatment guidelines recommend treatment of all HIV-infected patients irrespective of their CD4 count levels, with priority for patients with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with less than 350 CD4 T cells/μL (WHO, 2016). For many years, ART initiation was based on clinical examination and absolute CD4 T-cell counts (CD4 count) and thresholds of 500, 350 and 200 CD4 T cells/μL were used to initiate ART (WHO, 2013). However, the best disease-specific marker to monitor ART in HIV patients is plasma viral load (Phillips et al., 2015). Nevertheless CD4 remains the best measurement of a patient's immune and clinical status, risk of opportunistic infections, and it is being used to support diagnostic decision-making, particularly for patients with advanced HIV disease (Ford et al., 2017). As long as viral load testing is limited due to technical and financial constraints, it is expected that low-income regions will continue using CD4 counts as an alternative (Kahn et al., 2011).

2.15.2 Association of CD4 Cells with Cytopenias

HIV infection results in heightened systemic immune activation and inflammation, which predict more rapid CD4 cell decline and progression to AIDS and death, independent of plasma HIV RNA levels (Lederman et al., 2013). Overall, the incidence of hematological abnormalities increases with a decrease in CD4+ T-cell counts. Patients demonstrating a CD4+ T-cell count of <200 cells/μL are more likely to develop anemia, leukopenia, and neutropenia before the start of HAART medication (Duguma et al., 2021). However, Duguma et al reported that there was no significant association observed between hematological abnormalities and different categories of CD4+ T-cell counts in HIV-positive individuals on HAART (Duguma et al., 2021). In Africa, Studies carried out in Uganda and Ethiopia have reported a higher prevalence of thrombocytopenia in HIV infected patients with a CD4+ T lymphocyte count of <200 cells/μL (Marchionatti & Parisi, 2021).

It has been shown that the prevalence of anemia increases with decreasing CD4 count both before and after ART initiation with a high prevalence among patients with CD4 count < 200 cells/mm3 (Alamdo et al., 2015; Assefa et al., 2015; Tesfaye & Enawgaw, 2014; Dikshit et al., 2009). Studies conducted in African have reported that the highest rates of cytopenia occurred in patients with advanced HIV i.e. a CD4 count <200 cell/μl) (Kyeyune et al., 2014; De Santis et al., 2011; Dikshit et al., 2009; Subbaraman et al.,2009; Toure et al., 2006)

2.16 Impact of Antiretroviral Therapy on the Haematological and Immunological Abnormalities in HIV Infected Patients

2.16.1 Cytopenias

Initiation of ART has generally been regarded as the standard management for HIV/AIDS patients. Early use of HAART improves the clinical, hematological, and immunological profiles of patients, delays the progression of the disease, and improves survival of HIV-positive individuals, this later contributes to reducing viral transmission (Woldeamanuel & Wondimu, 2018; Group, 2017). In addition to the restoration of immunological function, ART has also been shown to improve HIV-related cytopenias, especially anaemia ((Harris et al., 2015; Johannessen et al., 2011; Odunukwe et al., 2005). A study by Johannessen et al (2011) recorded a reduction of anaemia from 77.4% among ART-naive patients to 38.2% after 12 months of ART (Johannessen et al., 2011). A study in Nigeria demonstrated a reduction in anaemia prevalence from 69.17% to 51.15% after ART (Omoregie et al., 2009). The decrease in the prevalence of anemia after HAART initiation is attributed to the positive effect of the treatment on the differentiation and survival of RBCs, decreases the viral load, and reduces the frequency of OIs (Fokouo et al., 2015), (Denue et al., 2013). Another study in Nigeria, by Denue et al (2013) also showed a significant improvement of haematological parameters with ART: the prevalence of anaemia was reduced from 57.5% pre-ART to 24.3% post- ART, while leucopenia and thrombocytopenia were reduced from 6.1% and 9.6% to 1.7% and 1.2%, respectively (Denue, et al., 2013). A study on the impact of HAART on haematological indices of HIV infected children in Kenya by Kibaru et al reported that hematological abnormalities changed significantly within 6 months of antiretroviral therapy with significant increase in hemoglobin level, MCV, MCH and platelet, however there was a decrease in WBC and RBC. It has been evidenced that HAART is an effective treatment for cytopenias such as anemia, thrombocytopenia, and neutropenia in HIV-1-infected patients (Duguma et al., 2021; Fan et al., 2020; Deressa et al., 2018; Woldeamanuel & Wondimu, 2018; Levine et al., 2006)**.** However the use of zidovudine (AZT)-containing ART regimens has been associated with high incidencies of anemia among HIV –infected patients receiving AZT-containing ART regimens (Kuwalairat & Winit-Watjana, 2014; Curkendall et al., 2007). Several studies have reported that HIV infected patients developed AZT –induced anemia after treatment with AZT-containing ART regimens (Dash et al., 2015), (Ikunaiye et al., 2018). This is because ZDV is mainly associated with myelotoxicity possibly by inhibiting erythroid precursor cells in the bone marrow leading to decreased RBC production manifesting in anemia (Marchionatti & Parisi, 2021; Agarwal et al., 2010; Berhane et al., 2020). On the contrary other studies have not found a significant association between treatment with AZT and anemia despite its frequent association with bone marrow suppression (Assefa et al., 2015; Kiragga et al., 2010; Renner et al., 2013).

It has been evidenced that a reduction in the prevalence of anemia is seen in HIV infected patients 6 months after initiation of ART (Alamdo et al., 2015; Gedefaw et al., 2013; Daka et al., 2013). In another study Cytopenia recovery rate was found to be 54% for anemia, 60.5% for thrombocytopenia, and 59.3% for previously lowered CD4+ T-cell count which improved after initiation of HAART. HAART initiation was found an effective treatment in reverting hematological abnormalities (especially cytopenias) in patients without treatment (Duguma et al., 2021).

2.17 Immunological Changes in HIV Infection

2.17.1 CD4 and CD8 Cell Counts

Untreated HIV infection is associated with decreases in CD4 count levels and increases in HIV plasma viral loads (Kaufmann et al., 2000). The initiation of ART is typically followed by declines in viral loads and increases in CD4 count. CD4 count recovery following ART initiation is rapid in the first few months, as a result of redistribution of the existing CD4 cells from lymphoid organs, and then slows down as new CD4 cells are made as a result of thymic activation (Gaardbo et al., 2012; Gazzola et al., 2009). The number of $CD4^{+}$T cells is maintained by the balance between their production and destruction, that is, when destruction exceeds production, the $CD4^{+}$T-cell counts declines (Gaardbo et al., 2013; Okoye & Picker, 2013). A number of factors are known to affect the extent of CD4 count recovery post ART initiation. These include CD4 count at ART initiation, gender -with males found to have lower CD4 recovery compared to females in some settings,(Maman et al., 2012) older age, (Simms et al., 2018; Fatti et al., 2014) duration on ART and ART regimen (He et al., 2016) as well as genetic and environmental factors that contribute to immune activation (Gazzola et al., 2009).

Previous studies revealed that $CD4^{+}$T-cell counts were higher in those participants who initiated ART earlier in comparison with those initiated ART later (Cao et al., 2015; Le et al., 2013). A study conducted in Goba Ethiopia found A CD4 recovery rate of 59.3% after initiation of HAART (Duguma et al., 2021)

Human immunodeficiency virus-1 (HIV-1) infection is characterized by gradual CD4 depletion, CD8 expansion, and immune activation (Mudd and Lederman, 2014). The dominant immunologic feature of HIV infection is progressive depletion of the helper T cell (CD4+ T cell), which reverses the normal CD4:CD8 ratio and subsequently lead to immunodeficiency. CD4+ T cells interact with antigen presenting cells (APCs), B cells, cytotoxic T cells (CD8+ T cells) as well as natural killer cells in order to clear the invading pathogens from the body. Thus, infection and depletion of CD4+ T cell population could induce profound immunodeficiency in such patients (Wan Mohamad et al., 2015). CD4 T cell responses are pivotal in the development of effective cellular and humoral immunity against viral infections (Morou, Palmer and Kaufmann, 2014). They lead to activation of naive B cells and plasma cells, which in turn secrete neutralizing and opsonizing antibodies (Swain, McKinstry and Strutt, 2012; Zhu and Paul, 2008). In addition, CD4 T cells induce macrophage activation, recruit phagocytes, primarily neutrophils and macrophages, to the site of infection, and stimulate activation of CD8 cytotoxic T cells -CTLs (Parham, 2014). Naive CD4+T cells are activated after interaction with antigen-MHC complex and differentiate into specific subtypes depending mainly on the cytokine milieu of the microenvironment. $CD4^{+}$T cells after being activated and differentiated into distinct effector subtypes play a major role in mediating immune response through the secretion of specific cytokines (Luckheeram et al., 2012).

2.18 Conceptual Framework

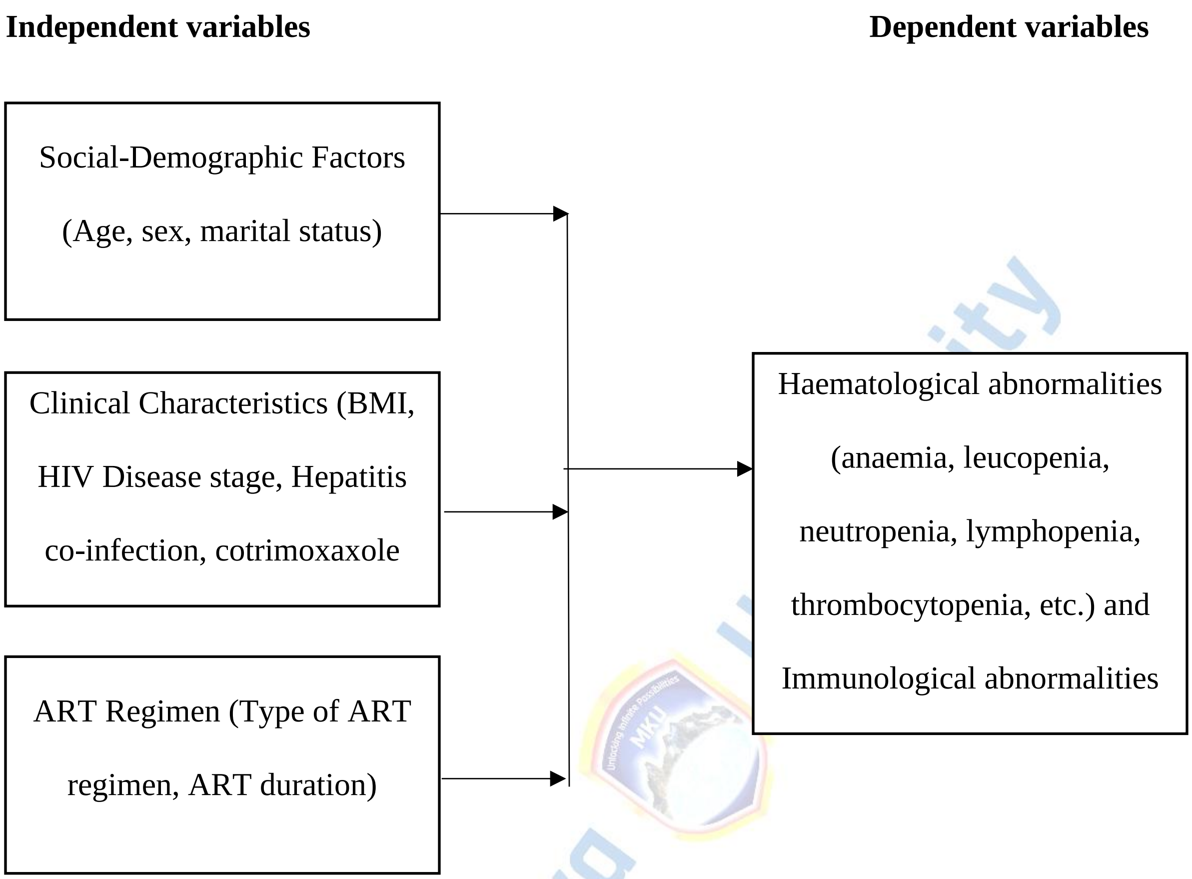

Figure 1: Conceptual Framework (Source: Literature review)

CHAPTER THREE

MATERIALS AND METHODS

3.1 Introduction

This facility – based cross sectional case – control study involved the HIV- infected patients attending Thika Level Five Hospital CCC from July 2022 to December 2023. The HIV infected patients included both the ART- naïve HIV-positive and ART-treated HIV positive patients and a control group of HIV- negative blood donors. The ART- naïve HIV- positive patients were those that were newly diagnosed at The Thika Level Five Hospital CCC either being referred to the Comprehensive Care Clinic for testing or those who visited the CCC for Voluntary Counselling and Testing for HIV. On the other hand, the ART- treated HIV positive patients are those who had already been previously diagnosed as HIV- positive and were already enrolled in to Thika Level Five Hospital CCC for treatment and care. Both ART- treated and ART-naïve were enrolled into the study after obtaining written informed consent (Appendix I). In addition, a control group of apparently healthy blood donors was also consented in to the study at the Thika blood satellite centre located at Thika Level Five Hospital (Appendix II).

The study was carried out at this facility since Thika Level Five Hospital is an inter-county referral facility with a high volume capacity comprehensive care center. In addition, the hospital has a wide catchment area that includes the neighbouring counties such as Machakos, Kitui, Muranga and Nairobi.

After consenting the study participants into the study (Appendix I), Patient assessment was first conducted to determine eligibility into the study. This was followed by collection of blood samples for laboratory analysis.

3.2 Study site

This study was conducted at the HIV Comprehensive Care Centre of Thika Level Five Hospital in Kiambu County, Kenya. Thika Level 5 Hospital is a County Referral Hospital located in Kiambu County, Thika Town Sub-County, Township Ward, along the General Kago Road. The hospital is a 467-bed capacity Government Hospital in the town of Thika, approximately 50 km north-east of Nairobi, in Central Province, Kenya. Kiambu county is the second most populous county after Nairobi with a population of 2,417,735 in an area of 2,539 km^2 and a Population Density of 952.4/km^2 (1). Thika Level Five Hospital is county referral facility with a wide catchment area that includes Machakos, Kitui, Muranga and Nairobi (Appendix IX). Thika Level Five Hospital is a Centre of Excellence offering comprehensive HIV and TB prevention, care and treatment services that include HIV testing, care and treatment, prevention of mother to child transmission of HIV, as well as maternal child health services.

Kiambu County has an estimated 59,016 people living with HIV, with an overall prevalence of 4.0 %, with a male prevalence of 2.1% and a female prevalence of 5.9%. By 2018, approximately 34417 adults and 1972 children were on ART with ART coverage of 61% and 82% for adults and children respectively (NASCOP, 2018).

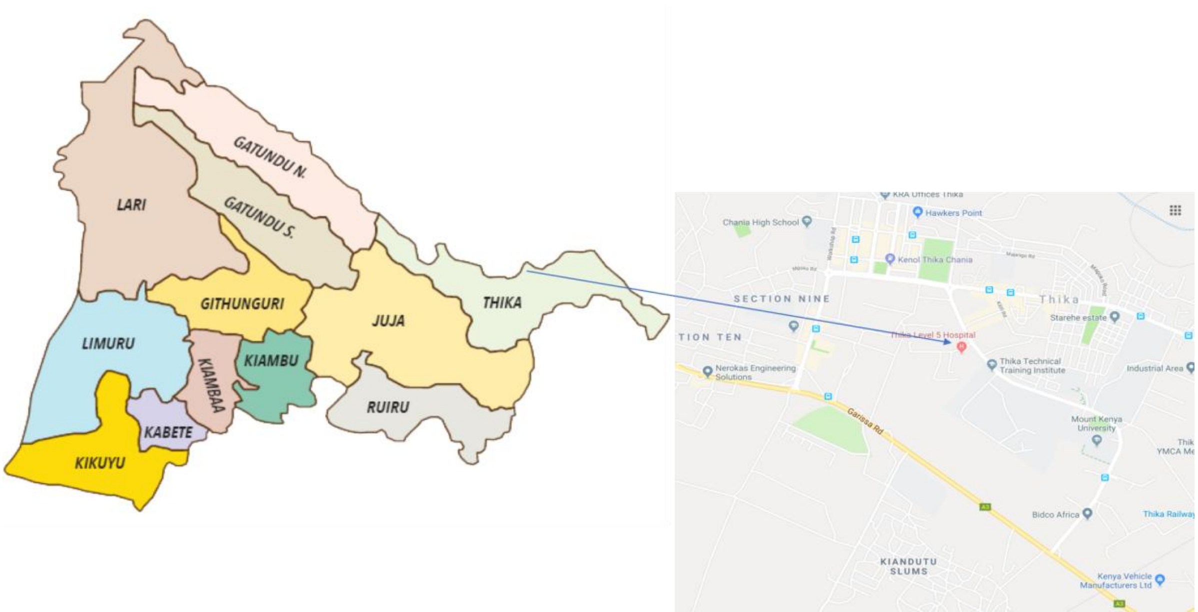

Figure 2: map of Kiambu County (Source: Gougle Maps)

3.3 Study Design

This was a hospital based case control cross-sectional study that was conducted from July 2022 to December 2023 at Thika Level Five Hospital CCC to assess the haematological and immunological abnormalities of HIV infected adult patients.

3.4 Study Population

The study population included all HIV infected patients who were already enrolled at the Thika Level Five Hospital CCC for treatment and care (ART-treated) and those who were newly diagnosed (ART- naïve) at the Thika Level Five Hospital CCC during the study period and who fulfilled the eligibility criteria. In addition, a control group of 80 HIV negative blood donors recruited at the Thika blood satellite centre were also enrolled into the study after obtaining of consent (Appendix II).

3.5 Sampling

3.5.1 Sample Size determination

The sample size was calculated by use of a single population proportional formula (Daniel, 2009).

Formula

n = N*X / (X + N – 1),

where,

$X = Z_{\alpha/2}^2 * p * (1-p) / MOE^2$,

$Z_{\alpha/2}$ = the critical value of the Normal distribution at α/2, thus, for a confidence level of 95%, α is 0.05 and the critical value is 1.96)

MOE = the margin of error = 5%

p is the sample proportion (proportion of HIV infected patients expected to have haematological abnormalities) =16% (Gathoni et al., 2015)

N is the population size =56,622

Therefore, by using 95% level of confidence (CI), 5%, margin of error, a prevalence of cytopenia of 16% from a previous study (Gathoni et al., 2015) and a population size of 56,622.

n = N*X / (X + N – 1),

=206 subjects

To account for non –response rate during the study, the sample size is adjusted by 15% thus the adjusted sample size is **237** subjects

The above 237 subjects are divided into two groups as follows:

HIV positive ART -naive HIV Patients =50

HIV positive ART -exposed HIV Patients =107

Control group of HIV negative healthy blood donors =80

3.5.2 Sampling procedure

The study participants were selected using simple random sampling technique at a sampling (K) interval of 21 until the required sample size was obtained. The sampling (K) interval was obtained by dividing the estimated population size of HIV-infected patients (5,000) by the total sample size (237)

3.6 Eligibility

3.6.1 Inclusion Criteria

1. HIV – positive individuals who are equal to or above 18 years of age
2. Patients consenting to this study

3.6.2 Exclusion Criteria

Study participants were excluded from the study if they were:

1. Below 18 years of age
2. Pregnant women
3. Patients who have had recent blood transfusion
4. Patients who have received chemotherapeutic agents within 6 months prior to enrollment
5. Patients with medication history (e.g. anti-tuberculosis drugs, antibiotics, ganciclovir, trimethoprim-sulfamethoxazole) or other drugs known to illicite cytopenia within 2 weeks before participant enrollment into the study.
6. Patients not consenting to this study
7. Patients with haematological disorders and those having severe concomitant diseases (opportunistic infections, cancer/malignancy etc.) at initiation or during the study period

3.7 Data Collection

From each of the participants enrolled the study, the first part of data collection involved patient assessment, collection of sociodemographic data and clinical characteristics of the study participants by use of a stuctured questionnaire (Appendix III) and the review of patient medical records. Socio-demographic data of the controls was also collected by use of a structured questionnaire (Appendix II). The questionnaire was pretested at Ruiru Level 4 Hospital by use of a 10% of the total sample size (237), which was a total of 24 patients prior to its use during the study.

The second part of data collection involved the collection of blood samples from the study participants and subsequent analysis of the haematological, immunological parameters and hepatitis testing. A clinician at the ART clinic, two experienced laboratory technologists and the principal investigator were involved in data collection. The principal investigator supervised the whole process.

3.7.1 Sociodemographic data and clinical characteristics

By use of a pretested structured questionnaire (Appendix III) the following information was collected: demographic characteristics (age, sex, marital status), clinical characteristics (concurrent medications on use, BMI, cotrimoxazole use, morbidities, type of Covid -19 vaccine) and ART information (type of ART regimen, duration on ART). The questionnaires were pre-tested by distributing the questionnaire to 24 HIV- infected patients.

3.7.2 Laboratory analysis

3.7.2.1 Sample collection and storage

After patient interview, two sets of 4 ml of EDTA anticoagulated venous blood was collected by the laboratory technologists from each study participant, one was used for haematological analysis of complete blood count (CBC) and immunologic (CD4 counts) while the other was separated into plasma and used for hepatitis A, B & C analysis

Serum samples were stored at minus (-) 40^0C at the Thika Level Five Hospital laboratory prior to use. The plasma samples were stored at minus (-) 40^0C until when samples from the whole cohort has been collected so as to analyze all the samples simultaneously. Also, samples were stored at minus (-) 40^{0C} until the completion of the research project.

3.7.2.2 Hematological, immunological and hepatitis analyses

HIV Testing

HIV testing was done by serial testing algorithm according to WHO testing protocols for HIV testing and the according to approved national testing algorithm 3.A, 3.B) For serial testing an initial blood sample is taken and tested. If the result is negative it is given. If the result is positive the blood sample is tested using a second, different HIV test. Patients visiting Thika Level Five Hospital HIV Comprehensive Care Centre for clinical diagnosis or voluntary testing were tested using two diagnostic rapid kits, which are Determine HIV 1/2 rapid diagnostic test kit (Abbott Diagnostic Division, Hoofddorp, The Netherlands) and First Response Test Card 1–2.0 (Premier Medical Corporation Ltd, India). The first screening test was with Determine HIV 1/2 RT; patients with a non-reactive test result were reported as HIV negative. Patients with a reactive result underwent confirmatory testing using a second rapid test (First Response HIV 1–2.0 Card Test [Premier Medical Corporation, Mumbai, India]). Those with a reactive result on both screening and confirmatory tests were classified as HIV positive.

To ensure accuracy and precision of the test results all the equipment used were calibrated before use and commercially acquired control materials run with the tests every time the samples were being analyzed.

HIV 1/2 assay by Determine

The protective cover on the strip was removed by tearing from the right. 50 µl of the whole blood sample was applied to the sample pad. When all the blood was absorbed into the sample pad, one drop of chase buffer was applied to the sample pad immediately. The results were read after 15 minutes.

First Response HIV 1–2.0 Card Test assay

The test card was labelled with the patient identification number and placed on a flat, clean and dry surface. Using the specimen transfer device, 20 ul of blood was drawn and added to the specimen well by gently touching the tips of the specimen transfer device to the sample pad. Holding the assay buffer vertically, one drop of assay buffer was then added to the specimen well. The results were read at 15 minutes after adding assay buffer by observation for development of purple colored lines in the results window.

Haematological and CD4 count analysis

For complete blood count (CBC) testing, EDTA anticoagulated venous blood sample was tested within one hour after collection using the fully automated hematology analyzer DYMIND DF-52 (DYMIND BIOTECH, China.). The EDTA anticoagulated whole blood sample was mixed thoroughly by gently inverting the sample tube. The sample tube was then placed under the probe and the start button was pressed. The aspirate key on the analyzer was pressed so as to start running the sample. The sample tube was removed when the status display changes from aspirating to running. The analyser generated data on the white blood cells (WBCs) including the 5 –part differentials (neutrophils, lymphocytes, monocytes, basophils and eosinophils), red blood cells (RBCs), haemoglobin level, haematocrit, mean cell volume(MCV), mean cell haemoglobin(MCH), mean cell haemoglobin concentration(MCHC), red cell distribution width (RDW), platelet counts, mean platelet volume (MPV), platelet distribution width, (PDW), plateletcrit (PCT),

The CD4+ T cells were assayed using EDTA the Becton Dickinson FACS Calibur system (Becton Dickinson, Singapore).

HAV Screening

Hepatitis A virus screening was done using Lumiquick HAV IgG/IgM Combo test card (Lumiquick Diagnostics Inc., Santa Clara, USA) that utilizes the principle of immuno-chromatography. The test cassette was allowed to reach room temperature before opening. Using the provided capillary pipette 2 µL of the plasma sample was pipetted and added to the sample bottle. The sample was then mixed with the buffer by gently shaking the bottle for a few times. The test cassette was removed from the foil and placed on a flat surface. Holding the bottle in a vertical position over the sample well of the test card, 2 drops (80 µL) of the test sample was added into the sample well marked S. The results were read at 20 minutes. The results were read as positive if a colored band appears in the test window in either IgG line/IgM line or both and a colored band in the Control line. Absence of a colored band in the test window indicated a negative test result.

HBV Screening

The plasma samples of the subjects were tested for the presence of Hepatitis B virus surface antigen (HBsAg) using Lumiquick commercial antigen-antibody test kits (Lumiquick Diagnostics Inc., Santa Clara, USA). This is an immunochromatography assay for the qualitative detection of hepatitis B virus surface antigens using the immunoassay based rapid test kits. For HBsAg testing, two drops (80µl) of plasma was dispensed onto the sample pad of the test strip. The results were read at 20 minutes after adding the sample. The results are read as positive if two colored bands appear within 20 minutes, one band in the Control Zone (C) and another colored band in the Test Zone (T) while only one colored bar in the control zone (C) and no colored band in the test zone (T) indicated negative results (Dowms et al., 2024; Davwar et al., 2023).

HCV Screening

HCV screening was done using commercially available Lumiquick HCV antibody test kits according to the manufacturer's instructions. Lumiquick HCV antibody test is a chromatographic immunoassay for qualitative detection of the antibodies against hepatitis C virus (HCV Ab) in human serum, plasma or whole blood samples. The test strip and the sample were allowed to reach room temperature before testing. Using the transfer pipette a drop (40µl) of the specimen was addaed to the sample pad on the test strip. The sample was let to be completely absorbed by the sample pad by waiting for a few seconds. Then one drop (40µl) of the sample buffer was added to the sample pad. The results were read at 20 minutes. The results were read as positive if two red colored bands, one in the Test Zone and the other in the Control Zone were visible within 20 minutes. Negative results were indicated if only one red line appears in the control zone (Bottero et al., 2013; Dowms et al., 2024).

Operational definitions

Anaemia was defined and graded according to the 2011 World Health Organization (WHO) report on Hb concentration level to diagnose anemia (WHO, 2011). Accordingly, for males, anaemia was defined as Hb concentration of <13 g/dL (11.0–12.9 g/dL as mild; 8.0– 10.9 g/ dL as moderate, and <8.0 g/dL as severe), whereas for females anaemia was defined as Hb concentration of <12.0 (11.0–11.9 g/ dL as mild, 8.0–10.9 g/ dL as moderate, and <8.0 g/dL as severe).

Leucopenia was defined as leucocyte count of $<4.0 \times 10^3/\mu L$, $4 – 11 \times 10^3/\mu L$ normal, and $>11 \times 10^3/\mu L$ as leucocytosis. Neutropenia was considered when absolute neutrophil counts (ANC) was $<1.5 \times 10^3/\mu L$. Lymphopenia was defined as absolute lymphocyte count (ALC) less than $< 1 \times 10^3/\mu L$.

Thrombocytopenia was defined as platelets counts $< 150 \times 10^3/\mu L$, which was further classified into mild thrombocytopenia ($100 – 149 \times 10^3/\mu L$), moderate thrombocytopenia ($50 – 99 \times 10^3/\mu L$), and severe thrombocytopenia ($< 50 \times 10^3/\mu L$).

Types of anemia were classified as normocytic (MCV 80 -100 fL), microcytic (MCV < 80 fL), macrocytic (MCV > 100 fL), normochromic (MCH ≥27 pg) and hypochromic (MCH < 27 pg).

Based on CD4 counts, the HIV infected patients were classified into three groups according to the Centers for Disease Control and Prevention (CDC) staging system. A CD4 count >500 cells/mm3 was considered stage 1, 200 to 499 cells/mm3 stage 2, and <200 cells/mm3 stage 3.

3.8 Data quality control

In order to ensure the quality of the data, the laboratory standard operating procedures (SOPs) were strictly followed during specimen collection and laboratory testing. The performance of haematology analyzer and the CD4 machine was controlled by running commercial quality control material alongside the study participant samples. Routine quality control checks for the equipment were carried out as per the manufacturer's instructions. Data collectors were trained prior to the start of the study and regular supervision and follow-up was done by the principal investigator. In addition, data was checked for completeness and consistency on a daily basis.

3.9 Statistical analysis

The data were coded, entered, cleaned, edited and entered into SPSS version 20 for analysis. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM, New York, USA). One-Way ANOVA with Tukey's post hoc was used for comparison of the hematological parameters of ART – naïve and ART –Treated & control group. A P- Value <0.05 was considered as statistically significant.

3.10 Data storage

The biological samples were stored for a period of not more than two years in $-40^{o}C$ at the Mount Kenya University research laboratory until project completion or publication of these findings. Upon completion of the study, these samples were disinfected with suitable disinfectant such as 10% Jik® and placed in red biohazard bags ready for incineration.

All paper research records were kept in locked filing cabinet located in a restricted-access room at the research station in Thika for the sample period and destroyed by shredding after study completion.

3.11 Data Management

All subjects were assigned a unique subject identification number (SID). The SID contained a serial number based on their enrollment dates. All data entered into the study databases was de-identified and only associated with a SID in password protected files. The study maintained a double entry system for the data. All paper research records were kept in locked filing cabinet located in a restricted-access room.

3.12 Ethical Considerations

Ethical clearance was obtained from the Institutional Ethics Review Board of Mount Kenya University, MKU/ERC/1013 (Appendix IV). An introductory letter to National Commission for Science, Technology and Innovation –NACOSTI (Appendix V) was obtained from the Directorate of Graduate Studies of Mount Kenya University which was used to apply for the research license from NACOSTI -NACOSTI/P/21/14506 (Appendix VI) before commencement of the study. Further approvals for conduction of the study at Thika Level Five Hospital CCC were obtained from the Health Research and Development Unit of Kiambu County (Appendix VII) and Permission to collect blood samples from the blood donors at the Thika Blood Satelite Center was also obtained from the Ministry of Health (MOH) before commencement of the study (Appendix VIII). The study participants were given full information about the study including its objectives, maintenance of confidentiality of their data and its use solely for research purposes. Written informed consent (Appendix I) was then obtained from all the participants before collecting blood samples. Participation in this study was completely voluntary and the participants were free to withdraw even after accepting to participate in the study.

3.13 Expected Outcomes

At least five (5) publications in peer reviewed journals as well as at least five (5) local conferences and a PhD thesis.

3.14 Mode of Dissemination of Research Findings

On completion of the study the research findings were disseminated through publishing in peer reviewed journals, presenting papers at national and international conferences as well as presenting the results to other local stakeholders.

CHAPTER FOUR

RESEARCH RESULTS AND DISCUSSIONS

4.0 Study Internal Quality Control Report

In order to ascertain the quality of the quantitative analytical work undertaken throughout the current study, internal quality control (IQC) specimens were analyzed before any analysis of the study subjects' specimens. The internal quality control specimen was analysed in 107 analytical sessions for the twelve haematological parameters. The study internal quality control range for each analyzed haematological parameter was a subset of the assigned internal quality control range for that specific parameter. The study internal quality control mean concentrations of each analyzed haematological parameter was equal or close to the assigned internal quality control mean concentration of each specific haematological parameter. Based on the study internal quality control report it can be ascertained that the current study qualitative analytical work was accurate and precise. The study internal quality report is expressed in **Table 1 and Table 2**

Table 1: The study internal quality control report for the analyzed haematological and immunological parameters

		Assigned IQC		Study IQC	
ANALYTE (UNITS)	**SESSION**	**RANGE**	**MEAN**	**RANGE**	**MEAN**
WBC (X10^3/µL)	107	6.9 – 8.9	7.9	7.48 - 8.49	8.01
NEUTROPHIL (X10^3/µL)	107	3.73 – 5.13	4.43	4.43 - 5.07	4.74
LYMPHOCYTE (X10^3/µL)	107	1.66 – 3.06	2.36	2.07 - 2.57	2.30
MONOCYTE (X10^3/µL)	107	0.03 - 1.03	0.53	0.44 - .67	0.52
RBC (X10^6/µL)	107	4.2 – 4.8	4.5	4.30 - 4.77	4.53
HB CONCENTRATION (g/dl)	107	7.0 – 19.0	13.0	12.4 - 12.7	12.5
HCT (%)	107	38.7 – 44.7	41.7	39.2 -43.0	40.8
MCV (femtolitres)	107	85.2 – 92.2	84.2	88.5 -91.9	90.0
MCH (Picograms)	107	25.7 – 30.7	28.2	26.5 -28.8	27.6
RDW (%)	107	14.1 – 20.1	17.1	15.2 -16.1	15.6
PLATELET (X10^3/µL)	107	225 - 305	265	245 -299	271.7
CD4 (cells/ µL)	107	565.6-848.4	707	570-830	700

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

4.1 Sociodemographic Characteristics of The Study Participants

In this study, a total of 237 study participants consisting of 106 ART - treated HIV infected adults, 51 ART - naive HIV infected adults and 80 HIV seronegative adult controls were enrolled into the study. The ART - naïve and ART - treated HIV infected adult patients were those who had either been newly diagnosed and enrolled or followed up for at least 6 months at the Thika Level Five Hospital Comprehensive Care Centre (CCC) from July 2022 to December, 2024.

The males formed the majority of the study participants 122 (51.48%) while females were 115 (48.52%) with a male to female ratio of 1.06:1. The age of the study participants ranged from 18 – 66 years with most of the study participants being 50 years and below. The majority of the study participants were in the 18-25 years' age group (31.65%) and ≥66 years were the least (0.42%). Most of the study participants were single (45.57%) with 43.88 % being married, 6.33% divorced, and 4.22% of them were widowed. Most of the study participants (65.1%) had normal weight with normal BMI, 3.36% were underweight, 28.18% were overweight and 3.36% were obese **(TABLE 3**).

Table 2: Demographic characteristics of the study population

Patient Factor		Frequency	Percentage (%)
Gender (n = 237)	Male	122	51.48
	Female	115	48.52
Age group (Years) (n = 237)	18-25	75	31.65
	26-35	64	27.00
	36-45	53	22.36
	46-55	27	11.39
	56-65	17	7.17
	≥66	1	0.42
Marital status (n = 237)	Single	108	45.57
	Married	104	43.88
	Divorced	15	6.33
	Widowed	10	4.22
Body Mass Index(BMI) (Kg/M^2) (HIV +ve only; n = 157)	<20	26	16.56
	21-25	84	53.50
	26-30	42	26.75
	>30	5	3.18

4.2 Descriptive Statistics

The mean and standard deviation of the haematological parameters for the ART – naïve, ART - treated HIV infected adult patients and controls were analysed as shown in the **Table 4**

In the present study, the mean total WBC levels of the ART – treated (5.40±1.46) and ART – naïve (5.24±2.71) HIV infected adult patients were lower than that of the control group (5.42 ±1.67). Similarly, the RBC levels of ART – treated (5.05±0.61) and ART – naïve (4.80±1.13) HIV infected adult patients were lower than that of the control group (5.29±0.42). The mean platelet count of the control group (322.50±118.40) was higher than that of the ART – treated (410.80±217.10) and ART – naïve (309.30±147.90) HIV infected adult patients. The absolute neutrophil count (ANC) of the control group (2.58±1.14) was lower than that of the ART – treated (2.89±1.48) and ART – naïve (3.55±2.55) HIV infected adult patients. The mean Total lymphocyte count of the control group (2.04±0.69) was higher than that of the ART – treated (1.99±0.63) and ART – naïve (1.50±0.66) HIV infected adult patients. The mean ± SD of HB of the control group (14.64±1.08) was higher than that of the ART – treated (13.96± 2.01) and ART – naïve (12.63±2.99) HIV infected adult patients. The mean ± SD of MCV of the ART – treated (90.35±10.48) was higher than for ART - naive ART (82.92±9.42) and the control group (88.93±5.20). The mean ± SD MCH of ART – treated HIV infected adult patients (27.76±3.18) were comparable to the mean ± SD MCH (27.73±1.74) of the controls but lower than the mean of ART – naïve HIV infected adult patients (25.83±3.50). The mean ± SD PCV of control group (46.97±3.21) was higher than that of the ART – treated (45.53±6.29) and the ART – naïve patients (40.57±9.13). The mean ± SD AMC (0.33±0.11) of the controls was lower compared to the mean ± SD AMC of ART – treated (0.41±0.13) and the ART – naïve (0.43±0.32). The mean ± SD RDW of ART – naïve (15.07±2.20) was higher than that of ART – treated (14.44±2.00) and the controls (14.47±0.85). The mean ± SD CD4 count of the control group (746.50±216.40) was higher than that of the ART – treated (378.50±317.7) and ART – naïve patients (348.50±256.90) **(Table 3)**

Table 3: Descriptive Statistics for Hematological and Immunological Parameters Selected

Parameter	ART-Treated (n = 106)	ART-Naïve (n = 51)	Control (n = 80)
WBC (×10^3/µL)	Mean = 5.40 SD= 1.46 95 % CI= 5.12-5.69	Mean= 5.24 SD= 2.71 95 % CI = 4.48-6.00	Mean = 5.42 SD = 1.67 95 % CI =5.05-5.80
RBC (×10^3/µL)	Mean = 5.05 SD = 0.61 95 % CI =4.93-5.12	Mean = 4.80 SD = 1.13 95 % CI = 4.53-5.17	Mean = 5.29 SD = 0.42 95 % CI = 5.20-5.39
Platelet count (×10^3/µL)	Mean= 410.80 SD =217.10 95 %CI = 369.0-452.6	Mean = 309.30 SD= 147.90 95 %CI = 369.00-452.60	Mean = 322.50 SD =118.40 95 % CI= 296.10-348.10
Neutrophil (× 10^3/µL)	Mean = 2.89 SD = 1.48 95 % CI = 2.61-3.17	Mean = 3.55 SD = 2.55 95 % CI = 2.83-4.27	Mean = 2.58 SD = 1.14 95 % CI = 2.33-2.83
Lymphocytes (×10^3/µL)	Mean = 2.03 SD = 0.66 95 % CI =1.90-2.16	Mean = 1.50 SD = 0.66 95 % CI =1.32-1.69	Mean = 2.04 SD = 0.69 95 % CI =1.88-2.19
HB (g/dL)	Mean = 13.96 SD = 2.01 95 % CI =13.57-14.34	Mean = 12.63 SD = 2.99 95 % CI =11.79-13.47	Mean = 14.64 SD = 1.08 95 % CI =14.40-14.88
MCV (fL)	Mean = 90.35 SD = 10.48 95 % CI =88.33-92.37	Mean = 82.92 SD = 9.42 95 % CI =80.27-85.57	Mean = 88.93 SD = 5.20 95 % CI =87.77-90.08
MCH (pg)	Mean = 27.76 SD = 3.18 95 % CI =27.14-28.37	Mean = 25.83 SD = 3.50 95 % CI =24.85-26.81	Mean = 27.71 SD = 1.74 95 % CI =27.32-28.09

Parameter	ART-Treated (n = 106)	ART-Naïve (n = 51)	Control (n = 80)
PCV (%)	Mean = 45.53 SD = 6.29 95 % CI =44.32-46.74	Mean = 40.57 SD = 9.13 95 % CI =38.00-43.14	Mean = 46.97 SD = 3.21 95 % CI =46.25-47.68
Monocyte ($\times 10^3/\mu L$)	Mean = 0.41 SD=0.13 95 %CI = 0.39-0.44	Mean = 0.43 SD=0.32 95 %CI = 0.34-0.52	Mean = 0.33 SD=0.11 95 %CI = 0.31-0.36
RDW	Mean =14.44 SD= 2.00 95 %CI= 14.05-14.82	Mean= 15.07 SD =2.20 95 %CI=14.45-15.69	Mean= 14.47 SD= 0.85 95 %CI= 14.28-14.66
CD_4 count (cells/µL)	Mean = 378.50 SD = 317.7 95 % CI =325.80-431.20	Mean = 348.50 SD = 256.90 95 % CI =276.20-420.70	Mean = 746.50 SD = 216.40 95 % CI =698.30-794.70

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

4.3 Objective 1: To Evaluate the Distribution and Magnitude of Haematological and immunological Abnormalities in the ART – Treated, ART – Naïve and the Control Group

Frequencies of the study participants who had the haematological abnormalities in the ART – treated, ART – naïve and the control group were analysed so as to evaluate the distribution of the haematological abnormalities across the groups. The frequencies of each of the haematological abnormality were then compared across the groups.

In the present study, 18.9% of the study participants had leucopenia. However, the frequency of leucopenia in ART – naïve adult patients was higher 25 (55.56%) than in ART – treated HIV patients 9 (20.00%) and the control group 11(24.44%).

Leukocytosis was seen in 1.3% of the study participants but it was higher in ART – naïve adult patients 2 (66.67%) than in ART – treated HIV patients 1(33.33%). There was no any case of leucocytosis in the control group 0 (0.00%).

The frequency of erythrocytopenia in ART – naïve adult patients was higher 6 (66.67%) than in ART – treated HIV patients 3 (33.33%). The frequency of erythrocytosis in ART – treated HIV patients was higher 5 (50.00%) than in ART – naïve adult patients 3 (30.00%) and the control group 2 (20.00%).

The frequency of moderate thrombocytopenia in ART – naïve adult patients was higher 2 (66.67 %) than in ART – treated HIV patients 1 (33.33 %). There was no any case of moderate thrombocytopenia in the controls 0 (0.00%). On the contrary, frequency of mild thrombocytopenia was higher in ART – naïve adult patients 2 (66.67 %) than in the control group 1 (33.33 %). There was no any case of mild thrombocytopenia in ART – treated HIV adult patients 0 (0.00%). Cases of thrombocytosis were higher in ART – treated HIV adult patients 28 (68.29 %) than in the ART – naïve adult patients 4 (9.76 %) and the controls 9 (21.95 %).

Overall, a total of 6 (46.15%) of the ART – treated HIV adult patients had neutropenia which is higher than that seen in ART – naïve adult patients 5 (38.46%) and the controls 2 (15.38%). More cases of mild neutropenia were seen in the ART – treated HIV adult patients 3 (42.86%) than in the ART – naïve adult patients 2 (28.57%) and the controls 2 (28.57%). Frequency of neutrophilia was higher in the ART – naïve adult patients 7 (58.33%) than in the ART – treated adult patients 4 (33.33%) and the controls 1 (8.33%).

Frequency of lymphopenia was higher in the ART – naïve adult patients 10 (62.50%) than in the ART – treated adult patients 4 (25.00%) and the controls 2 (12.50%). There was only one case of lymphocytosis which was seen in the ART – treated patients with a frequency of 1 (100%). Lymphocytosis was not seen in the ART – naïve and control group.

There was no any case of monocytopenia in the ART – treated adult patients 0 (0.00%) while the frequency of monocytopenia was higher in the ART – naïve adult patients 6 (60.00%) than in the controls 4 (40.00%).

There was no any case of severe and mild anemia in the controls 0 (0.00%), however the frequency of severe anemia in the ART – naïve adult patients and the ART – treated adult patients was equal 1 (50.00%). More cases of mild anemia were seen in the ART – naïve adult patients 6 (54.55%) than in the ART – treated adult patients 5 (45.45%). Similarly, more cases of low haematocrit was seen in the ART – treated adult patients 27 (50.94%) than in the ART – naïve adult patients 26 (49.06%). There was no any case of low haematocrit in the controls 0 (0.00%). Similarly, more cases of high haematocrit were seen in the ART – treated adult patients 8 (61.54%) than in the ART – naïve adult patients 3 (23.08%) and controls 2 (15.38%). The controls had the lowest frequency of microcytosis 4 (12.50%) while the frequency of microcytosis in ART – naïve adult patients and the ART – treated adult patients was equal 14 (43.75%). There was no any case of macrocytosis in the controls 0 (0.00%), however it was higher in the ART – treated adult patients 23 (69.70%) than in the ART – naïve adult patients 10 (30.30%). Frequency of hypochromia was higher in the ART – naïve adult patients 29 (39.19%) than in the ART – treated adult patients 22 (29.73%) and the controls 23 (31.08%). Additionally, more cases of elevated RDW was seen in the ART – naïve adult patients 11 (44.00%) than in the ART – treated adult patients 9 (36.00%) and the controls 5 (20.00%).

Most of the study participants 125 (52.7%) had CD4 count >500cells/μL (Stage I) with a frequency of 44 (35.20 %), 8 (6.40 %) and 73 (66.00 %) in ART –treated, ART – naïve and controls respectively. A total of 37.1% of the study participants had CD4 count between 200 -499 cells/ μL (Stage II) which also varied among the ART – treated, ART – naïve and the control with a frequency of 53 (60.23 %), 28 (31.82 %) and 7 (7.95 %). Only 24 (10.1%) of the study participants had CD4 count of <200 cells/ μL with a frequency of 8 (33.33 %) and 16 (66.67 %) in ART – treated and ART – naïve patients respectively. there was no any case of immunosuppression (CD4 count of <200 cells/ μL) in the control group.

Table 4: Frequency Distribution and Magnitude of Hematological and Immunological Abnormalities in ART –Treated, ART –Naïve and Controls

Parameter	**Abnormality**	**ART-Treated (n = 106)**		**ART-Naïve (n = 51)**		**Control (n = 80)**	
		Frequency	Prevalence	Frequency	Prevalence	Frequency	Prevalence
WBC (× 10^3/μL)	Leukopenia (n= 45)	9 (20.00%)	8.5%	25 (55.56%)	49.0%	11(24.44%)	13.7%
	Normal WBC (n = 189)	86(45.50%)		29 (15.34%)		74 (39.15%)	
	Leukocytosis (n = 3)	1(33.33%)	0.94%	2 (66.67%)	3.92%	0 (0.00%)	0%
RBC (× 10^3/μL)	Erythropenia (n = 9)	3 (33.33%)	2.83%	6 (66.67%)	11.8%	0 (0.00%)	0%
	Normal RBC (n = 218)	98 (44.45%)		42 (19.27%)		78 (35.78%)	
	Erythrocytosis (n= 10)	5 (50.00%)	4.7%	3 (30.00%)	5.9%	2 (20.00%)	2.5%
Platelet count (× 10^3/μL)	Thrombocytopenia (n = 6)	1 (16.66%)	0.94%	4 (66.67 %)	7.84%	1 (16.66%)	1.25%
	Moderate thrombocytopenia (n = 3)	1 (33.33 %)		2 (66.67 %)		0 (0.00 %)	

Parameter	Abnormality	ART-Treated (n = 106)		ART-Naïve (n = 51)		Control (n = 80)	
	Mild thrombocytopenia (n =3)	0 (0.00 %)		2 (66.67 %)		1 (33.33 %)	
	Normal PLT (n =190)	77 (40.53 %)		43 (22.63 %)		70 (36.84 %)	
	Thrombocytosis (n=41)	28 (68.29 %)	26.4%	4 (9.76 %)	7.84%	9 (21.95 %)	11.25%
Neutrophil (× $10^3/\mu L$)	Neutropenia (n= 29)	16 (55.18 %)	15.1%	9 (31.03 %)	17.6%	4 (13.79 %)	5%
	Mild Neutropenia (n= 21)	12(57.15 %)		7 (33.33 %)		2(9.52 %)	
	Moderate Neutropenia (n= 8)	4 (50.00 %)		2 (25.00 %)		2 (25.00 %)	
	Normal neutrophil count (n=200)	88 (44.00%)		37 (18.50 %)		75 (37.50 %)	
	Neutrophilic leukocytosis (n=8)	2 (25.00 %)	1.9%	5 (62.50 %)	9.8%	1 (12.50 %)	1.25%
Lymphocytes (× $10^3/\mu L$)	Lymphopenia (n=18)	4 (22.22%)	3.8%	12 (66.67%)	23.6%	2 (1.11%)	2.5%
	Normal lymphocyte (n=218)	101 (46.33%)		39 (17.89%)		78 (35.78%)	
	Lymphocytosis (n=1)	1 (100%)	0.94%	0 (0.00%)	0%	0 (0.00%)	0%
Monocytes	Monocytopenia (n =12)	0 (0.00%)	0%	7 (58.33 %)	13.7%	5 (41.67 %)	6.25%
	Normal Monocyte count (n= 219)	105 (47.95 %)		39 (18.72 %)		70 (33.33 %)	
	Monocytosis (n=6)	1 (16.67 %)	0.94%	5 (83.33 %)	9.8%	0 (0.00 %)	0%
HB (g/dL)	Anemia (n= 36)	16 (44.44 %)	15.1%	20 (55.56 %)	39.2%	0 (0.00 %)	0%
	Severe Anemia (n= 4)	3 (75.00 %)		1 (25.00 %)		0 (0.00 %)	
	Mild Anemia (n= 14)	7 (50.00 %)		7 (50.00 %)		0 (0.00%)	

Parameter	**Abnormality**	**ART-Treated (n = 106)**		**ART-Naïve (n = 51)**		**Control (n = 80)**	
	Moderate Anemia (n=18)	6 (33.33 %)		12 (66.67 %)		0 (0.00 %)	
	Normal HB (n=201)	93 (46.27 %)		33 (16.42 %)		75 (37.31 %)	
HCT	Low HCT (n=53)	27 (50.94%)	25.4%	26 (49.06%)	50.9%	0 (0.00%)	0%
	Normal HCT (n=171)	61 (35.67%)		38 (22.22%)		72 (42.11%)	
	High HCT (n=13)	8 (61.54%)	7.55%	3 (23.08%)	5.88%	2 (15.38%)	2.5%
MCV (fL)	Microcytosis (n=32)	14 (43.75%)	13.2%	14 (43.75%)	27.5%	4 (12.50%)	5%
	Normocytic Anemia (n= 172)	60 (34.88%)		36 (20.93%)		76 (44.19%)	
	Macrocytosis (n= 33)	23 (69.70%)	48.3%	10 (30.30%)	19.6%	0 (0.00%)	0%
MCH (pg)	Normochromia (n =140)	63 (45.00 %)		21 (15.00 %)		56 (40.00 %)	
	Hypochromia (n = 88)	34 (38.64 %)	32.1%	30 (34.09 %)	58.8%	24 (27.27 %)	30%
	Hyperchromia (n = 9)	9 (100%)	8.5%	0 (0.00%)	0%	0 (0.00%)	0%
RDW	Normal RDW (n= 208)	96 (46.15%)		37 (17.79 %)		75 (36.06%)	
	High RDW (n= 29)	10 (34.48 %)	9.4%	14 (48.28 %)	27.5%	5 (17.24 %)	6.25%
CD_4 count	>500cells/µL(n=125)	44 (35.20 %)	41.5%	8 (6.40 %)	15.6%	73 (66.00 %)	91.3%
	200 to 499 cells/ µL (n= 88)	53 (60.23 %)	50%	28 (31.82 %)	54.9%	7 (7.95 %)	8.75%
	<200 cells/ µL (n=24)	8 (33.33 %)	7.5%	16 (66.67 %)	31.4%	0 (0.00%)	0%

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

4.4 Objective 2: To Compare the Haematological and Immunological Parameters between the ART – treated and ART – naïve HIV infected patients

To compare the haematological and immunological parameters between the ART – treated and ART – naïve HIV infected patients, unpaired T – test and the Welch's correction was used for statistical analysis at 95% C.I at a p- value of 0.05. Results on table 6 shows that there was significant difference in the mean ± SD of the PLT, ALC, HB, MCV, MCH and PCV of the ART – treated compared to the ART – naïve HIV infected patients. However, there was no significant difference in the mean ± SD of the WBC, RBC, ANC, AMC, RDW and CD4 Count of the ART – treated and ART – naïve HIV infected patients. The mean ± SD of platelet count (410.80±217.10) of ART – treated was significantly higher compared with mean platelet count (309.30±147.90) of ART – naïve HIV infected patients ($p = 0.0030$). The mean ± SD ALC (2.03±0.66) of ART – treated was significantly higher compared with mean ALC (1.50±0.66) of ART – naïve HIV infected patients ($p < 0.0001$). The mean ± SD HB (13.96± 2.01) of ART – treated was significantly higher compared with mean HB (12.63±2.99) of ART – naïve HIV infected patients ($p = 0.0054$). The mean ± SD MCV (90.35±10.48) of ART – treated was significantly higher compared with mean MCV (82.92±9.42) of ART – naïve HIV infected patients ($p < 0.0001$). The mean ± SD MCH (27.76±3.18) of ART – treated was significantly higher compared with mean MCH (25.83±3.50) of ART – naïve HIV infected patients ($p = 0.0013$). The mean ± SD PCV (45.53±6.29) of ART – treated was significantly higher compared with mean PCV (40.57±9.13) of ART – naïve HIV infected patients (p =0.0008). The mean ± SD AMC (0.41±0.13) of ART – treated was significantly higher compared with mean AMC (0.43±0.32) of ART – naïve HIV infected patients (p =0.6676). The mean ± SD RDW (14.44±2.00) of ART – treated was lower compared with mean RDW (15.07±2.20) of ART – naïve HIV infected patients but not significantly different (p =0.0855). The mean ± SD CD4 count (378.50±317.7) of ART – treated was higher compared to mean ± SD CD4 count (348.50±256.90) of ART – naïve HIV infected patients but not significantly different (p =0.5045). **Table 5**

Table 5: Comparison of Haematological and Immunological Parameters of ART –Treated and ART – Naïve Patients

Parameter	ART-Treated	ART-Naïve	*t* (df)	P value
WBC (× 10^3/µL)	5.40±1.46	5.24±2.71	0.4843 (155)	0.6289
RBC (× 10^3/µL)	5.05±0.61	4.80±1.13	1.407 (155)	0.1615
PLT count (× 10^3/µL)	410.80±217.10	309.30±147.90	3.016 (155)	0.0030
ANC (× 10^3/µL)	2.89±1.48	3.55±2.55	1.720 (66.26)	0.0901
ALC (× 10^3/µL)	2.03±0.66	1.50±0.66	4.643 (98.57)	<0.0001
HB (g/dL)	13.96± 2.01	12.63±2.99	2.868 (72.41)	0.0054
MCV (fL)	90.35±10.48	82.92±9.42	4.461 (109.0)	<0.0001
MCH (pg)	27.76±3.18	25.83±3.50	3.3290 (90.85)	0.0013
PCV (%)	45.53±6.29	40.57±9.13	3.50 (73.62)	0.0008
AMC (× 10^3/µL)	0.41±0.13	0.43±0.32	0.4317 (58.43)	0.6676
RDW	14.44±2.00	15.07±2.20	1.7390 (90.83)	0.0855
CD_4 count (cells/µL)	378.50±317.7	348.50±256.90	0.6697 (108.4)	0.5045

Values are presented as $\overline{x \pm SD}$. Unpaired student t-tests with Welch's correction at $\alpha_{0.05}$

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

4.5 Objective 3: Hematological and Immunological Abnormalities in HIV Infected Patients on ART in relation to the type of ART regimen

Fishers test was used to find out if there is a relationship between the haematological and immunological abnormalities in HIV infected adult patients on ART in relation to the type of ART regimen. Statistical analysis was done at 95% C.I at A p-value 0.05. As shown in table 7, the ART regimen significantly influenced the ALC, HCT, MCV, MCH, RDW and HIV disease stage abnormalities of the ART – treated HIV infected patients. ART regimen significantly normalized the ALC of ART – treated HIV infected patients. ART – treated patients who were on TDF/3TC/DTG had significantly higher cases of lymphopenia than those on AZT/3TC/ATV/r and ABC/3TC/ATV/r regimens (P = 0.0252). On the contrary ART – treated patients on TDF/3TC/ATV/r and AZT/3TC/DTG regimens did not present with lymphopenia (P = 0.0252). The ART regimen significantly influenced the HCT abnormalities of the ART – treated HIV infected patients with those on AZT/3TC/ATV/r showing significantly higher 12 (100.00 %) cases of low HCT (P = <0.0001). ART – treated patients on TDF/3TC/DTG had significantly higher 7 (53.85 %) cases of high HCT than those on other types of ART (P = <0.0001). There was significantly higher microcytosis 17 (100.00 %) in those taking AZT/3TC/ATV/r than the other ART regimens (P = <0.0001). Similarly, there was significantly higher 6 (35.29 %) macrocytosis in those on AZT/3TC/ATV/r and TDF/3TC/DTG than 2 (11.76 %) TDF/3TC/ATV/r, 1 (5.88 %) ABC/3TC/ATV/r and 2 (11.76 %) AZT/3TC/DTG (P = <0.0001). Hypochromia was significantly higher 32 (94.12 %) in those taking TDF/3TC/DTG than 2 (5.88 %) in those on AZT/3TC/ATV/r (P = 0.0268). There was a significantly higher 6 (60.00 %) RDW in those ART –treated patients on TDF/3TC/DTG than 3 (30.00%) in those on AZT/3TC/ATV/r and

1 (10.00 %) in those on ABC/3TC/ATV/r (p = 0.0044). ART regimen significantly influenced the HIV disease stage of HIV - treated patients with those on AZT/3TC/DTG having significantly higher 36 (81.82 %) stage I HIV disease than 6 (13.64 %) for TDF/3TC/ATV/r and 2 (4.55 %) for those on AZT/3TC/ATV/r (P = <0.0001) while TDF/3TC/DTG had significantly higher stage II HIV disease 41 (77.36 %) and stage III HIV disease 7 (87.50 %) (P = <0.0001). The ART regimen did not significantly influence the WBC, RBC, PLT, ANC, AMC, and HB abnormalities. (**Table 6)**

Table 6: Hematological and immunological abnormalities of ART - treated patients in relation to the type of ART regimen

Abnormality if present		ART Regimen					P value
		AZT/3TC/ATV/r	**TDF/3TC/DTG (TLD)**	**TDF/3TC/ATV/r**	**ABC/3TC/ATV/r**	**AZT/3TC/DTG**	
WBC	Leucopenia (n= 19)	1 (5.26 %)	17 (89.47 %)	0 (0.00%)	1 (5.26%)	0 (0.00%)	0.2475
	Normal (n= 85)	5 (5.88 %)	66 (77.65 %)	12 (14.12 %)	0 (0.00 %)	2 (2.35 %)	
	Leukocytosis (n= 1)	0 (0.00 %)	1 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
RBC	Anemia (n= 1)	1 (33.33 %)	2 (66.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0.5214
	Normal RBC (n= 5)	0 (0.00 %)	5 (100 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
	Erythrocytosis (n=98)	6 (6.12 %)	77 (78.57 %)	12 (12.24 %)	1 (1.02 %)	2 (2.04 %)	
PLT	Mild thrombocytopenia (n= 0)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0.0800
	Moderate thrombocytopenia (n= 1)	0 (0.00 %)	1 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
	Normal PLT (n = 76)	6 (7.89 %)	56 (73.68 %)	12 (15.79 %)	1 (1.32 %	1 (1.32 %)	

Abnormality if present		ART Regimen					P value
		AZT/3TC/ATV/r	TDF/3TC/DTG (TLD)	TDF/3TC/ATV/r	ABC/3TC/ATV/r	AZT/3TC/DTG	
	Thrombocytosis (n= 28)	0 (0.00 %)	27 (96.43 %)	0 (0.00 %)	0 (0.00 %)	1 (3.57)	
ANC	Neutropenia (n=12)	0 (0.00 %)	12 (100 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0.7537
	Moderate neutropenia (n= 4)	0 (0.00 %)	4 (100 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
	Normal neutrophil (n =84)	6 (7.14 %)	64 (76.19 %)	11 (13.10 %)	1 (1.19 %)	2 (2.38 %)	
	Neutrophilia (n =5)	1 (20.00%)	4 (80.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
ALC	Lymphopenia (n= 4)	1 (25.00%)	2 (50.00 %)	0 (0.00 %)	1 (25.00%)	0 (0.00 %)	0.0252
	Normal (n= 101)	6 (5.94 %)	82 (81.19 %)	11 (10.89 %)	0 (0.00 %)	2 (1.98 %)	
AMC	Normal (n =103)	6 (5.83 %)	83 (80.58 %)	11 (10.68 %)	1 (0.97 %)	2 (1.94 %)	>0.9999
	Monocytosis (n =1)	0 (0.00 %)	1 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
Hb	Severe anemia (n= 2)	0 (0.00 %)	2 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0.8660

Abnormality if present		**ART Regimen**					**P value**
		AZT/3TC/ATV/r	**TDF/3TC/DTG (TLD)**	**TDF/3TC/ATV/r**	**ABC/3TC/ATV/r**	**AZT/3TC/DTG**	
	Mild anemia (n= 7)	0 (0.00 %)	7 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
	Moderate anemia (n = 6)	1 (16.67 %)	5 (83.33 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	
	Normal Hb (n= 89)	6 (6.74 %)	70 (78.65 %)	10 (11.24 %)	1 (1.12 %)	2 (2.25 %)	
HCT	Low HCT (n =12)	12 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	<0.0001
	Normal HCT (n =79)	3 (3.80 %)	65 (82.28 %)	10 (12.66 %)	0 (0.00 %)	1 (1.27 %)	
	High HCT (n =13)	4 (30.77 %)	7 (53.85 %)	0 (0.00 %)	1 (7.69 %)	1 (7.69 %)	
MCV	Microcytosis (n =17)	0 (0.00 %)	0 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	<0.0001
	Normocytosis (n= 72)	1 (1.39 %)	61 (84.72 %)	10 (13.89 %)	0 (0.00 %)	0 (0.00 %)	
	Macrocytosis (n= 17)	9 (52.94 %)	5 (29.41 %)	(0.00 %)	1 (5.88 %)	2 (11.76 %)	
MCH	Normochromia (n =71)	4 (5.63 %)	52 (73.24 %)	12 (16.90 %)	1 (1.41 %)	2 (2.82 %)	0.0268
	Hypochromia (n =34)	2 (5.88 %)	32 (94.12 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	

Abnormality if present		ART Regimen					P value
		AZT/3TC/ATV/r	**TDF/3TC/DTG (TLD)**	**TDF/3TC/ATV/r**	**ABC/3TC/ATV/r**	**AZT/3TC/DTG**	
RDW	Normal RDW (n = 95)	3 (3.16 %)	78 (72.11 %)	12 (12.63 %)	0 (0.00 %)	2 (2.11 %)	0.0044
	High RDW (n= 10)	3 (30.00%)	6 (60.00 %)	0 (0.00 %)	1 (10.00 %)	0 (0.00 %)	
CD_4 count	CD4>500 cells/µL) (n =44)	2 (4.55 %)	0 (0.00 %)	6 (13.64 %)	0 (0.00 %)	36 (81.82 %)	<0.0001
	CD4 200 to 499 cells/µL (n =53)	4 (7.55 %)	41 (77.36 %)	6 (11.32 %)	0 (0.00 %)	2 (3.77 %)	
	CD4< 200 cells/µL (n= 8)	0 (0.00 %)	7 (87.50 %)	0 (0.00 %)	1 (12.50 %)	0 (0.00 %)	

Fisher's exact test; $\alpha_{0.05}$

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

4.6 Objective 4: Association of sociodemographic factors and clinical characteristics with haematological abnormalities in HIV infected patients at Thika Level 5 Hospital

To determine if there is an association between the haematological and immunological abnormalities and the sociodemographic factors and clinical characteristics of the study subjects, analysis was done using fisher's exact test was used at a 95% C.I, p – value 0.05.

In this study, it was demonstrated that patient gender did not have a significant influence on the WBC, RBC, PLT, ANC, ALC, AMC, HCT, MCV and RDW abnormalities of the study subjects (p-value > 0.05). However, patient gender had significant influence on the HB and MCH abnormality, with females having a significantly higher HB abnormality (p-value = 0.0021) and MCH abnormality (p-value = 0.0050) than the males. (**Table 7**)

Table 7: Association between the Haematological Abnormalities and Patient Gender

Hematological parameter	Abnormality	Patient gender		P value
		Male	Female	
WBC	Present (n = 34)	18 (52.94 %)	16 (47.06 %)	0.2667
	Absent (n = 56)	37 (66.07 %)	19 (33.93 %)	
RBC	Present (n = 15)	8 (53.33 %)	7 (46.67 %)	0.5673
	Absent (n = 75)	47 (62.67 %)	28 (37.33 %)	
PLT	Present (n = 37)	16 (43.24 %)	21 (56.76 %)	0.2429
	Absent (n =120)	39 (32.50 %)	81 (67.50%)	
ANC	Present (n =26)	16 (61.54 %)	10 (38.46 %)	>0.9999
	Absent (n = 64)	39 (60.94 %)	25 (39.06 %)	
ALC	Present (n = 12)	5 (41.67 %)	7 (58.33 %)	0.1899
	Absent (n = 52)	34 (65.38 %)	18 (35.06 %)	
AMC	Present (n = 13)	5 (38.46 %)	8 (61.54 %)	0.1214
	Absent (n = 77)	50 (64.94 %)	27 (35.06 %)	
Hb	Present (n = 22)	7 (31.82 %)	15 (68.18 %)	0.0021
	Absent (n = 68)	48 (70.59 %)	20 (29.41 %)	
HCT	Present (n = 35)	20 (57.14 %)	15 (42.86 %)	0.6580
	Absent (n = 55)	35 (63.64 %)	20 (36.36 %)	
MCV	Present (n = 27)	16 (59.26 %)	11 (40.74 %)	0.8179
	Absent (n = 63)	39 (61.90 %)	24 (38.10 %)	
MCH	Present (n = 42)	19 (45.24 %)	23 (54.76 %)	0.0050
	Absent (n = 48)	36 (75.00 %)	12 (25.00 %)	
RDW	Present (n = 17)	7 (41.18 %)	10 (58.82 %)	0.0958
	Absent (n = 73)	48 (65.75 %)	25 (34.25 %)	

Fisher's exact test; $\alpha_{0.05}$.

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

The results of the present study demonstrated that patient age significantly influenced the PLT abnormality (p-value = 0.003) and HCT abnormality (p-value = 0.0472) of the study subjects. The study subjects aged 18 – 25 years were more prone to the PLT abnormality 19 (51.35 %) than the other age groups while those aged between 26 – 35 years were more likely affected by the HCT abnormality 10 (30.30 %). On the other hand, the WBC, RBC, ANC, ALC, AMC, HB, MCV, MCH and RDW were not significantly influenced by patient age (p-value > 0.05). (**Table 8)**

Table 8: Association between the Haematological Abnormalities and Patient Age

Hematological parameter	**Abnormality**	**Age group (Years)**						**P value**
		18-25	**26-35**	**36-45**	**46-55**	**56-65**	**>66**	
WBC	Present (n = 34)	7 (20.59 %)	11 (32.35 %)	9 (26.47 %)	3 (8.82 %)	4 (11.76 %)	0 (0.00%)	0.0650
	Absent (n = 56)	25 (44.64 %)	11 (19.64 %)	14 (25.00 %)	5 (8.93 %)	1 (1.79 %)	0 (0.00%)	
RBC	Present (n= 15)	6 (40.00 %)	4 (26.67 %)	3 (20.00 %)	2 (13.33 %)	0 (0.00 %)	0 (0.00%)	0.8294
	Absent (n= 75)	26 (34.67 %)	18 (24.00%)	20 (26.67 %)	6 (8.00%)	5 (6.67 %)	0 (0.00%)	
PLT	Present (n = 37)	19 (51.35 %)	4 (10.81 %)	5 (13.51 %)	7 (18.92 %)	2 (5.41 %)	0 (0.00 %)	0.0030
	Absent (n = 119)	24 (20.17 %)	27 (22.69 %)	39 (32.77 %)	15 (12.61 %)	13 (10.92 %)	1 (0.84 %)	
ANC	Present (n = 29)	11 (37.93 %)	5 (17.24 %)	6 (20.69 %)	3 (10.34 %)	4 (13.79 %)	0 (0.00%)	0.6117

Hematological parameter	Abnormality	Age group (Years)						P value
		18-25	**26-35**	**36-45**	**46-55**	**56-65**	**>66**	
	Absent (n = 64)	21 (32.81 %)	17 (26.56 %)	17 (26.56 %)	5 (7.81 %)	4 (6.25 %)	0 (0.00%)	
ALC	Present (n = 16)	2 (12.50 %)	5 (31.25 %)	7 (43.75 %)	1 (6.25 %)	1 (6.25 %)	0 (0.00%)	0.1398
	Absent (n = 74)	30 (40.54 %)	17 (22.97 %)	16 (21.62 %)	7 (9.46 %)	4 (5.41 %)	0 (0.00%)	
AMC	Present (n = 13)	4 (30.77 %)	5 (38.46 %)	2 (15.38 %)	1 (7.69 %)	1 (7.69 %)	0 (0.00%)	0.6492
	Absent (n = 77)	28 (36.36 %)	17 (22.08 %)	21 (27.27 %)	7 (9.09 %)	4 (5.19 %)	0 (0.00%)	
Hb	Present (n = 22)	6 (27.27 %)	8 (36.36 %_	5 (22.73 %)	2 (9.09 %)	1 (4.55 %)	0 (0.00%)	0.6637
	Absent (n = 68)	26 (38.24 %)	14 (20.59 %)	18 (26.47 %)	6 (8.82 %)	4 (5.88 %)	0 (0.00%)	
HCT	Present (n = 33)	7 (21.21 %)	10 (30.30 %)	7 (21.21 %)	5 (15.15 %)	4 (12.12 %)	0 (0.00%)	0.0472
	Absent (n = 55)	23 (41.82 %)	12 (21.82 %)	16 (29.09 %)	3 (5.45 %)	1 (1.82 %)	0 (0.00%)	
MCV	Present (n = 27)	8 (29.63 %)	5 (18.52 %)	8 (29.63 %)	5 (18.52 %)	1 (3.70 %)	0 (0.00%)	0.2731
	Absent (n = 63)	24 (38.10 %)	17 (26.98 %)	15 (23.81 %)	3 (4.76 %)	4 (6.35 %)	0 (0.00%)	
MCH	Present (n = 42)	16 (38.10 %)	13 (30.95 %)	7 (16.67 %)	5 (11.90 %)	1 (2.38 %)	0 (0.00%)	0.1966

Hematological parameter	Abnormality	Age group (Years)						P value
		18-25	26-35	36-45	46-55	56-65	>66	
	Absent (n = 48)	16 (33.33 %)	9 (18.75 %)	16 (33.33 %)	3 (6.25 %)	4 (8.33 %)	0 (0.00%)	
RDW	Present (n = 17)	4 (23.53 %)	6 (35.29 %)	4 (23.53 %)	1 (5.88 %)	2 (11.76 %)	0 (0.00%)	0.4284
	Absent (n = 73)	28 (38.36 %)	16 (21.92 %)	19 (26.03 %)	7 (9.59 %)	3 (4.11 %)	0 (0.00%)	

Fisher's exact test; $\alpha_{0.05}$.

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

The present study results demonstrated marital status did not have a significant influence on the WBC, RBC, PLT, ALC, AMC, HB, PCV, MCV, MCH and RDW abnormality. However, marital status significantly influenced the ANC abnormality of the study subjects p-value = 0.0004). The single HIV infected study subjects were more likely affected 16 (48.48 %) by the ANC abnormality than the married 9 (27.27 %), divorced 7 (21.21 %) and widowed 1 (3.03 %)HIV infected subjects. **(Table 9)**

Table 9: Association between the Haematological Abnormalities and Marital status

Hematological parameter	Abnormality	Marital status				P-value
		Single	Married	Divorced	Widowed	
WBC	Present (n =34)	15 (44.12 %)	17 (50.00 %)	2 (5.88 %)	0 (0.00 %)	0.5986
	Absent (n =56)	30 (53.57 %)	20 (35.71 %)	5 (8.93 %)	1 (1.79 %)	

Hematological parameter	Abnormality	Marital status				P-value
		Single	Married	Divorced	Widowed	
RBC	Present (n = 15)	8 (53.33 %)	5 (33.33 %)	1 (6.67 %)	1 (6.67 %)	0.2665
	Absent (n= 75)	37 (49.33 %)	32 (42.67 %)	6 (8.00 %)	0 (0.00%)	
PLT	Present (n =37)	21 (56.76 %)	14 (37.84%)	2 (5.41 %)	0 (0.00 %)	0.0660
	Absent (n =120)	43 (35.83 %)	54 (45.00 %)	13 (10.83 %)	10 (8.33 %)	
ANC	Present (n =33)	16 (48.48 %)	9 (27.27 %)	7 (21.21 %)	1 (3.03 %)	0.0004
	Absent (n =57)	29 (50.88 %)	28 (49.12 %)	0 (0.00 %)	0 (0.00 %)	
ALC	Present (n =16)	5 (31.25 %)	10 (62.50 %)	1 (6.25 %)	0 (0.00 %)	0.2775
	Absent (n =74)	40 (54.05 %)	27 (36.49 %)	6 (8.11 %)	1 (1.35 %)	
AMC	Present (n= 13)	9 (69.23 %)	4 (30.77 %)	0 (0.00 %)	0 (0.00 %)	0.4285
	Absent (n= 77)	36 (46.75 %)	33 (42.86 %)	7 (9.09 %)	1 (1.30 %)	
Hb	Present (n = 22)	11 (50.00 %)	10 (4.55 %)	1 (45.45 %)	0 (0.00 %)	0.9033
	Absent (n = 68)	34 (50.00 %)	27 (39.71 %)	6 (8.82 %)	1 (1.47 %)	

Hematological parameter	Abnormality	Marital status				P-value
		Single	Married	Divorced	Widowed	
HCT	Present (n= 35)	18 (51.43 %)	14 (40.00%)	3 (8.57 %)	0 (0.00 %)	>0.9999
	Absent (n= 55)	27 (49.09 %)	23 (41.82 %)	4 (7.27 %)	1 (1.82%)	
MCV	Present (n = 27)	16 (59.26 %)	9 (33.33 %)	1 (3.70 %)	1 (3.70 %)	0.2411
	Absent (n = 63)	29 (46.03 %)	28 (44.44 %)	6 (9.52 %)	0 (0.00 %)	
MCH	Present (n =42)	24 (57.14 %)	13 (30.95 %)	4 (9.52 %)	1 (2.38 %)	0.2043
	Absent (n = 48)	21 (43.75 %)	24 (50.00 %)	3 (6.25 %)	0 (0.00 %)	
RDW	Present (n =17)	9 (52.94 %)	8 (47.06 %)	0 (0.00 %)	0 (0.00 %)	0.6359
	Absent (n= 73)	36 (49.32 %	29 (39.73 %)	7 (9.59 %)	1 (1.37 %)	

Fisher's exact test; $\alpha_{0.05}$.

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

The present study finding showed that patient BMI significantly influenced the WBC abnormality (p-value = 0.0223) with a BMI range of 20 - 25 15 Kg/M^2 being more prone 15 (44.12 %) to the WBC abnormality. Similarly, patient BMI significantly influenced the MCV abnormality (p-value

= 0.041) of the study subjects with those in the range of 20 - 25 15 Kg/M^2 being more prone 19 (90.48 %) to the MCV abnormality. On the contrary, patient BMI did not significantly influence the RBC, PLT, ANC, ALC, AMC, HB, HCT, MCH and RDW of the study subjects (p-value > 0.05). **(Table 11)**

Table 10: Association between the Haematological Abnormalities and Patient BMI

Hematological parameter	**Abnormality**	**BMI (Kg/M^2)**				**P-value**
		<20	**20-25**	**26-30**	**>30**	
WBC	Present (n =34)	13 (38.24 %)	15 (44.12 %)	5 (14.71 %)	1 (2.94 %)	0.0223
	Absent (n =56)	9 (16.67 %)	40 (71.43 %)	7 (14.71 %)	0 (0.00 %)	
RBC	Present (n = 15)	5 (33.33)	10 (66.67 %)	0 (0.00 %)	0 (0.00 %)	0.3743
	Absent (n= 75)	17 (22.67 %)	45 (60.00 %)	12 (16.00 %)	1 (1.33%)	
PLT	Present (n =37)	7 (18.92 %)	22 (59.46 %)	8 (21.62 %)	0 (0.00 %)	0.5802
	Absent (n =120)	19 (15.83 %)	62 (51.67 %)	34 (28.33 %)	5 (4.17 %)	
ANC	Present (n =26)	9 (34.62 %)	15 (57.69 %)	2 (7.69 %)	0 (0.00 %)	0.4589
	Absent (n =64)	13 (20.31 %)	40 (62.50 %)	10 (15.63 %)	1 (1.56 %)	
ALC	Present (n =16)	4 (25.00 %)	12 (75.00 %)	0 (0.00 %)	0 (0.00 %)	0.3628
	Absent (n =74)	18 (24.32 %)	43 (58.11 %)	12 (16.22 %)	1 (1.30 %)	
AMC	Present (n= 13)	4 (30.77 %)	7 (53.85 %)	2 (15.38 %)	0 (0.00 %)	0.7882
	Absent (n= 77)	18 (23.38 %)	48 (62.34 %)	10 (12.99 %)	1 (1.30 %)	
Hb	Present (n = 22)	7 (31.82 %)	14 (63.64 %)	1 (4.55 %)	0 (0.00 %)	0.4820
	Absent (n = 68)	15 (22.06 %)	41 (60.29 %)	11 (16.18 %)	1 (1.47 %)	
HCT	Present (n= 30)	4 (13.33 %)	23 (76.67 %)	3 (10.00 %)	0 (0.00 %)	0.6404
	Absent (n= 51)	9 (17.65 %)	32 (62.75 %)	9 (17.65 %)	1 (1.96 %)	
MCV	Present (n = 21)	1 (4.76 %)	19 (90.48 %)	1 (4.76 %)	0 (0.00 %)	0.0411
	Absent (n = 63)	15 (23.81 %)	36 (57.14 %)	11 (17.46 %)	1 (1.59 %)	

Hematological parameter	Abnormality	BMI (Kg/M²)				P-value
		<20	20-25	26-30	>30	
MCH	Present (n =42)	12 (28.57 %)	24 (57.14 %)	5 (11.90 %)	1 (2.38 %)	0.6445
	Absent (n = 48)	10 (20.83 %)	31 (64.58 %)	7 (14.58 %)	0 (0.00 %)	
RDW	Present (n= 17)	6 (35.29 %)	10 (58.82 %)	1 (5.88 %)	0 (0.00 %)	0.5590
	Absent (n =73)	16 (21.92 %)	45 (61.64 %)	11 (15.07 %)	1 (1.37 %)	

Fisher's exact test; $\alpha_{0.05}$.

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

The findings from the present study demonstrated that cotrimoxazole use significantly influenced the RBC abnormality of the study subjects (p – value = 0.0262) with those not on cotrimoxazole use being more prone to the RBC abnormality. All study subjects who were not on cotrimoxazole did not have any RBC abnormality. However, cotrimoxazole use did not significantly influence the WBC, PLT, ANC, ALC, AMC, HB, HCT, MCV, MCH and RDW of the study subjects (p-value > 0.05). **(Table 11)**

Table 11: Association between the Haematological Abnormalities and Cotrimoxazole Use

Hematological parameter	Abnormality	Cotrimoxazole use	No cotrimoxazole use	P value
WBC	Present (n = 34)	0 (0.00 %)	34 (100.00 %)	0.5246
	Absent (n = 56)	2 (3.57 %)	54 (96.43 %)	
RBC	Present (n = 15)	2 (13.33 %)	13 (86.67 %)	0.0262
	Absent (n =)	0 (0.00 %)	75 (100.00 %)	
PLT	Present (n = 37)	1 (2.70 %)	36 (97.30 %)	>0.9999
	Absent (n =120)	5 (4.17 %)	115 (95.83 %)	

Hematological parameter	Abnormality	Cotrimoxazole use	No cotrimoxazole use	P value
ANC	Present (n =26)	2 (7.69 %)	24 (92.31 %)	0.0811
	Absent (n =64)	00 (0.00 %)	64 (100.00 %)	
ALC	Present (n =16)	1 (6.25 %)	15 (93.75 %)	0.3256
	Absent (n =74)	1 (1.35 %)	73 (98.65 %)	
AMC	Present (n = 13)	0 (0.00 %)	13 (100.00 %)	>0.9999
	Absent (n = 77)	2 (2.60 %)	75 (97.40 %)	
Hb	Present (n = 22)	1 (4.55 %)	21 (95.45 %)	0.4312
	Absent (n = 68)	1 (1.47 %)	67 (98.53 %)	
HCT	Present (n = 35)	0 (0.00 %)	35 (100.00 %)	0.5194
	Absent (n = 55)	2 (3.64 %)	53 (96.36 %)	
MCV	Present (n =27)	1 (3.70 %)	26 (96.30 %)	0.5124
	Absent (n =63)	1 (1.59 %)	62 (98.41 %)	
MCH	Present (n =42)	1 (2.38 %)	41 (97.62 %)	>0.9999
	Absent (n =48)	1 (2.08 %)	47 (97.92 %)	
RDW	Present (n =17)	0 (0.00 %)	17 (100.00 %)	>0.9999
	Absent (n =72)	1 (1.39 %)	71 (98.61 %)	

Fisher's exact test; $\alpha_{0.05}$.

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

The present study results indicate that hepatitis A, B, C – HIV co-infection did not significantly influence the WBC, RBC, PLT, ANC, ALC, AMC, HB, HCT, MCV, MCH and RDW abnormalities of the study subjects (p-value > 0.05). **Table 12**

Table 12: Association between the Haematological Abnormalities and Hepatitis A, B and C (Hep) Co-infection

Hematological parameter	Abnormality	Hepatitis co-infection						P value
		Hep-A+ve	Hep-A-ve	Hep-B+ve	Hep-B-ve	Hep-C+ve	Hep-C-ve	
WBC	Present (n =102)	2 (1.96 %)	32 (31.37 %)	1 (0.98 %)	33 (32.35 %)	1 (0.98 %)	33 (32.35 %)	0.8926
	Absent (n =168)	5 (2.98 %)	51 (30.36 %)	1 (0.60 %)	55 (32.74 %)	0 (0.00 %)	56 (33.33 %)	
RBC	Present (n = 45)	1 (2.22 %)	14 (31.11 %)	0 (0.00 %)	15 (33.33 %)	1 (2.22 %)	14 (31.11 %)	0.5299
	Absent (n =225)	6 (2.67 %)	69 (30.67 %)	2 (0.89 %)	73 (32.44 %)	0 (0.00 %)	75 (33.33 %)	
PLT	Present (n = 111)	3 (2.70 %)	34 (30.63 %)	2 (1.80 %)	35 (31.53 %)	1 (0.90 %)	36 (32.43 %)	0.6358
	Absent (n = 360)	8 (2.22 %)	112 (31.11 %)	2 (1.80 %)	118 (31.53 %)	1 (0.28 %)	119 (33.06 %)	
ANC	Present (n =77)	4 (5.19 %)	22 (28.57 %)	2 (2.60 %)	24 (31.17 %)	0 (0.00 %)	25 (32.47 %)	0.1503
	Absent (n = 192)	3 (1.56 %)	61 (31.77 %)	0 (0.00 %)	64 (33.33 %	1 (0.52 %)	63 (32.81 %)	
ALC	Present (n =48)	1 (2.08 %)	15 (31.25 %)	0 (0.00 %)	16 (33.33 %)	1 (0.00 %)	15 (31.25 %)	0.5571
	Absent (n =223)	7 (3.14 %)	68 (30.49 %)	2 (0.90 %)	72 (32.29 %)	0 (0.00 %)	74 (33.18 %)	

Hematological parameter	Abnormality	Hepatitis co-infection						P value
		Hep-A+ve	Hep-A-ve	Hep-B+ve	Hep-B-ve	Hep-C+ve	Hep-C-ve	
AMC	Present (n = 39)	0 (0.00 %)	13 (33.33 %	0 (0.00 %)	13 (33.33 %)	1 (2.56 %)	12 (30.77 %)	0.3881
	Absent (n = 231)	7 (3.03 %)	70 (30.30%)	2 (0.87 %)	75 (32.47 %)	0 (0.00 %)	77 (33.33 %)	
Hb	Present (n = 66)	2 (3.03 %)	20 (30.30 %)	1 (1.52 %)	21 (31.82 %)	1 (1.52 %)	21 (31.82 %)	0.5262
	Absent (n =204)	5 (2.45 %)	63 (30.88 %)	1 (0.49 %)	67 (32.84 %)	0 (0.00 %)	68 (33.33 %)	
HCT	Present (n = 105)	2 (1.90 %)	33 (21.43 %)	1 (0.95 %)	34 (32.38 %)	1 (0.95 %)	34 (33.33 %)	0.8982
	Absent (n = 165)	5 (3.03 %)	50 (30.30 %)	1 (0.61 %)	54 (32.73 %)	0 (0.00 %)	55 (33.33 %)	
MCV	Present (n = 81)	2 (2.47 %)	25 (30.86 %)	1 (1.23 %)	26 (32.10 %)	1 (1.23 %)	26 (32.10 %)	0.7280
	Absent (n = 189)	5 (2.65 %)	58 (30.69 %)	1 (0.53 %)	62 (32.80 %)	0 (0.00 %)	63 (33.33 %)	
MCH	Present (n =118)	3 (2.54 %)	32 (27.12 %)	1 (0.85 %)	40 (33.90 %)	1 (0.85 %)	41 (34.75 %)	0.8622
	Absent (n = 144)	4 (2.78 %)	44 (30.56 %)	0 (0.00 %)	48 (33.33 %)	0 (0.00 %)	48 (33.33 %)	
RDW	Present (n =51)	1 (1.96 %)	16 (31.37 %)	1 (1.96 %)	16 (31.37 %)	1 (1.96 %)	16 (31.37 %)	0.3657

Hematological parameter	Abnormality	Hepatitis co-infection						P value
		Hep-A+ve	Hep-A-ve	Hep-B+ve	Hep-B-ve	Hep-C+ve	Hep-C-ve	
	Absent (n =219)	6 (2.74 %)	67 (30.59 %)	1 (0.46 %)	72 (32.88 %)	0 (0.00 %)	73 (33.33 %)	

Fisher's exact test; $\alpha_{0.05}$.

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

The results of this study demonstrated that ART duration significantly influenced the WBC abnormality of the study subjects (p-value = 0.0125). Those ART – treated HIV infected patients on ART duration of 16 -20 years were more prone to WBC abnormality 4 (40.00 %) than those on 11-15 Years (30.30 %), 6-10 Years (30.00 %) 1-5 Years (0.00 %) and <1 Year (0.00 %). Similarly, ART duration significantly influenced the ALC abnormality of the study subjects (p-value <0.0001) with those on ART for 11-15 Years being more significantly affected (76.47 %) by ALC abnormality than 16 -20 years, 1-5 Years, and <1 Year duration with a frequency of (5.88 %), 11.76 %, 0.00 % and 5.88 % respectively. In addition, ART duration significantly influenced the HCT abnormality of the study subjects (p-value = 0.0310) with those on ART for 6 – 10 years being more significantly affected (71.43 %) than 16 -20 years, 11-15 Years,1 – 5 years and <1 Year duration with a frequency of 14.29 %, 7.14 %, 7.14 % and 0.00 % respectively. However, ART duration did not significantly influence the RBC, PLT, ANC, AMC, HB, MCV, MCH and RDW OF THE HIV – infected study subjects (p-value > 0.05) **Table 13.**

Table 13: Association between the Haematological Abnormalities and ART Duration

Haematological parameter	Abnormality	ART duration (Years)					
		<1 Yr	1-5 Yrs	6-10 Yrs	11-15 Yrs	16-20 yrs	P value
WBC	Present (n = 10)	0 (0.00 %)	0 (0.00 %)	3 (30.00 %)	3 (30.30 %)	4 (40.00 %)	0.0125
	Absent (n = 29)	1 (3.45 %)	3 (1.34 %)	15 (51.72 %)	10 (34.48 %)	0 (0.00 %)	
RBC	Present (n =6)	2 (33.33 %)	0 (0.00 %)	3 (50.00 %)	1 (16.67 %)	0 (0.00 %)	0.0618
	Absent (n= 34 %)	0 (0.00 %)	3 (8.82 %)	15 (44.12 %)	12 (35.39 %)	4 (11.76 %)	
PLT	Present (n =9)	0 (0.00 %)	1 (11.11 %)	3 (33.33 %)	5 (55.56 %)	0 (0.00 %)	0.4605
	Absent (n =30)	2 (6.67 %)	2 (6.67 %)	15 (50.00 %)	8 (26.67 %)	3 (10.00 %)	
ANC	Present (n = 11)	2 (18.18 %)	0 (0.00 %)	4 (36.36 %)	4 (36.36 %)	1 (9.09 %)	0.2135
	Absent (n =30)	0 (0.00 %)	3 (10.00 %)	14 (46.67 %)	10 (33.33 %)	3 (10.00 %)	

Haematological parameter	Abnormality	ART duration (Years)					
		<1 Yr	1-5 Yrs	6-10 Yrs	11-15 Yrs	16-20 yrs	P value
ALC	Present (n =17)	1 (5.88 %)	0 (0.00 %)	2 (11.76 %)	13 (76.47 %)	1 (5.88 %)	<0.0001
	Absent (n = 24)	1 (4.17 %)	3 (12.50 %)	16 (66.67 %)	0 (0.00 %)	4 (16.67 %)	
AMC	Present (n= 1)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (100.00 %)	0 (0.00 %)	0.5500
	Absent (n =39)	2 (5.13 %)	3 (7.69 %)	18 (46.15 %)	12 (30.77 %)	4 (10.26 %)	
Hb	Present (n = 3)	1 (33.33 %)	0 (0.00 %)	2 (66.67 %)	0 (0.00 %)	0 (0.00 %)	0.2209
	Absent (n = 37)	1 (2.70 %)	3 (8.11 %)	16 (43.24 %)	13 (35.14 %)	4 (10.81 %)	
HCT	Present (n =14)	0 (0.00 %)	1 (7.14 %)	10 (71.43 %)	1 (7.14 %)	2 (14.29 %)	0.0310
	Absent (n =26)	2 (7.69 %)	2 (7.69 %)	8 (30.77 %)	12 (46.15 %)	2 (7.69 %)	
MCV	Present (n =11)	1 (9.09 %)	0 (0.00 %)	8 (72.73 %)	1 (9.09 %)	1 (9.09 %)	0.1089

Haematological parameter	Abnormality	ART duration (Years)					
		<1 Yr	1-5 Yrs	6-10 Yrs	11-15 Yrs	16-20 yrs	P value
	Absent (n = 29)	1 (3.45 %)	3 (10.34 %)	10 (34.48 %)	12 (41.38 %)	3 (10.81 %)	
MCH	Present (n = 12)	1 (8.33 %)	1 (8.33 %)	6 (50.00 %)	4 (33.33 %)	0 (0.00 %)	0.7414
	Absent (n = 28)	1 (3.57 %)	2 (7.14 %)	12 (42.86 %)	9 (32.14 %)	4 (14.29 %)	
RDW	Present (n =3)	0 (0.00 %)	0 (0.00 %)	2 (66.67 %)	0 (0.00 %)	1 (33.33 %)	0.4082
	Absent (n =37)	2 (5.41 %)	3 (8.11 %)	16 (43.24 %)	13 (35.14 %)	3 (8.11 %)	

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

Results on table 14 show that HIV disease stage significantly influenced the PLT count (p value = 0.0012) of the study subjects with those at HIV disease stage II being more affected (51.35 %) by the PLT abnormality than those at stage I (48.65 %). However, WBC, RBC, ANC, ALC, AMC, HB, HCT, MCV, MCH and RDW abnormalities were not significantly affected by the HIV disease stage (p-value > 0.05).

Table 14: Association between the Haematological Abnormalities and HIV Disease Stage

Hematological parameter	Abnormality	HIV staged based on the CD4 cell count			P value
		Stage 1 (>500cells/µL)	Stage 2 (200-499cells/µL)	Stage 3 (<200 cells/µL)	
WBC	Present (n =10)	3 (30.00 %)	5 (50.00 %)	2 (20.00 %)	0.4848
	Absent (n =30)	9 (30.00 %)	19 (63.33 %)	2 (6.67 %)	
RBC	Present (n = 6)	2 (33.33 %)	4 (66.67 %)	0 (0.00 %)	>0.9999
	Absent (n = 34)	10 (29.41 %)	20 (56.82 %)	4 (11.76 %)	
PLT	Present (n =37)	18 (48.65 %)	19 (51.35 %)	0 (0.00 %)	0.0012
	Absent (n =119)	34 (28.57 %)	61 (51.26 %)	24 (20.17 %)	
ANC	Present (n =19)	10 (52.63 %)	8 (42.11 %)	1 (5.26 %)	0.6112
	Absent (n =31)	12 (38.71 %)	16 (51.61 %)	3 (9.68 %)	
ALC	Present (n =4)	0 (0.00 %)	3 (75.00 %)	1 (25.00 %)	0.2737
	Absent (n =36)	12 (33.33 %)	21 (58.33 %)	3 (8.33 %)	
AMC	Present (n =1)	0 (0.00 %)	1 (100.00 %)	0 (0.00 %)	>0.9999
	Absent (n =39)	12 (30.77 %)	23 (58.97 %)	4 (10.26 %)	
Hb	Present (n =3)	0 (0.00 %)	3 (100.00 %)	0 (0.00 %)	0.6648

Hematological parameter	Abnormality	HIV staged based on the CD4 cell count			P value
		Stage 1 (>500cells/µL)	**Stage 2 (200-499cells/µL)**	**Stage 3 (<200 cells/µL)**	
	Absent (n =37)	12 (32.43 %)	21 (56.76 %)	4 (10.81 %)	
HCT	Present (n =14)	4 (28.57 %)	8 (57.14 %)	2 (14.29 %)	0.7880
	Absent (n =26)	8 (30.77 %)	16 (61.54 %)	2 (7.69 %)	
MCV	Present (n =11)	4 (36.36 %)	6 (54.55 %)	1 (9.09 %)	0.8683
	Absent (n =29)	8 (27.59 %)	18 (62.07 %	3 (10.34 %)	
MCH	Present (n =13)	4 (30.77 %)	8 (61.54 %)	1 (7.69 %)	>0.9999
	Absent (n =27)	8 (29.63 %)	16 (59.26 %)	3 (11.11 %)	
RDW	Present (n =1)	0 (0.00 %)	2 (66.67 %)	1 (33.33 %)	0.1830
	Absent (n =37)	12 (32.43 %)	22 (59.46 %)	3 (8.11 %)	

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

Results on table 15 demonstrate that Covid -19 vaccine type significantly influenced PLT abnormality (p value = 0.0401). Non Covid – 19 vaccinated HIV – infected patients were more significantly affected by PLT abnormality 23 (62.16 %) than the Covid – 19 vaccinated HIV – infected patients. However, for ART – treated HIV – infected patients, those on AstraZeneca and Johnson & Johnson were more significantly affected by the PLT abnormality than those on, Moderna and Pfizer Covid vaccine types with frequencies of 13.51 %, 13.51 %, 2.70 % and 8.11 % respectively. Similarly, Covid -19 vaccine type significantly influenced ANC abnormality (p value = 0.0010) with those HIV patients not Covid – 19 vaccinated being more significantly affected 13 (86.67 %) by the ANC abnormality than the Covid – 19 vaccinated HIV – infected patients. In addition, those on Johnson & Johnson had significantly higher 7 (17.07 %) ANC abnormality than those on AstraZeneca 4 (9.76 %), Moderna 2 (4.88 %) and Pfizer 3 (7.32 %).

Table 16: Association between the Haematological Abnormalities and COVID-19 Vaccine Type

Parameter	Abnormality	COVID-19 Vaccine Type					P value
		AstraZeneca	Johnson & Johnson	Moderna	Pfizer	None	
WBC	Present (n = 45)	5 (11.11 %)	2 (4.44 %)	3 (6.67 %)	1 (2.22 %)	34 (75.56 %)	0.6927
	Absent (n =112)	22 (19.64 %)	6 (5.36 %)	6 (5.36 %)	5 (4.46 %)	73 (65.18 %)	
RBC	Present (n = 17)	2 (11.76 %)	0 (0.00 %)	0 (0.00 %)	1 (5.88 %)	14 (82.35 %)	0.6427
	Absent (n = 140)	25 (17.86 %)	8 (5.71 %)	9 (6.43 %)	5 (3.57 %)	93 (66.43 %)	
PLT	Present (n = 37)	5 (13.51 %)	5 (13.51 %)	1 (2.70 %)	3 (8.11 %)	23 (62.16 %)	0.0401
	Absent (n = 120)	22 18.33 %)	3 (2.50 %)	8 (6.67 %)	3 (2.50 %)	84 (70.00 %)	
ANC	Present (n = 41)	4 (9.76 %)	7 (17.07 %)	2 (4.88 %)	3 (7.32 %)	25 (60.98 %)	0.0010

Parameter	Abnormality	COVID-19 Vaccine Type					P value
		AstraZeneca	Johnson & Johnson	Moderna	Pfizer	None	
	Absent (n = 116)	23 (19.83 %)	1 (0.86 %)	7 (6.03 %)	3 (2.59 %)	82 (70.69 %)	
ALC	Present (n =15)	0 (0.00 %)	0 (0.00 %)	2 (13.33 %)	0 (0.00 %)	13 (86.67 %)	0.1540
	Absent (n = 141)	26 (18.44 %)	8 (5.67 %)	7 (4.96 %)	6 (4.26 %)	94 (66.67 %)	
AMC	Present (n = 15)	3 (20.00 %)	0 (0.00 %)	2 (13.33 %)	0 (0.00 %)	10 (66.67 %)	0.5834
	Absent (n = 142)	24 (16.90 %)	8 (5.63 %)	7 (4.93 %)	6 (4.23 %)	97 (68.31 %)	
Hb	Present (n = 31)	4 (12.90 %)	0 (0.00 %)	0 (0.00 %)	1 (3.23 %)	26 (83.87 %)	0.4546
	Absent (n =100)	6 (6.00 %)	2 (2.00 %)	6 (6.00 %)	5 (5.00 %)	81 (81.00 %)	
HCT	Present (n = 48)	5 (10.42 %)	3 (6.25 %)	4 (8.33 %)	1 (2.08 %)	35 (72.92 %)	0.4569

Parameter	Abnormality	COVID-19 Vaccine Type					P value
		AstraZeneca	Johnson & Johnson	Moderna	Pfizer	None	
	Absent (n = 109)	22 (20.18 %)	5 (4.59 %)	5 (4.59 %)	5 (4.59 %)	72 (66.06 %)	
MCV	Present (n = 50)	7 (14.00 %)	0 (0.00 %)	5 (10.00 %)	3 (6.00 %)	35 (70.00 %)	0.0939
	Absent (n = 107)	20 (18.69 %)	8 (7.48 %)	4 (3.74 %)	3 (2.80 %)	72 (67.29 %)	
MCH	Present (n = 64)	10 (15.63 %)	0 (0.00 %)	4 (6.25 %)	2 (3.13 %)	48 (75.00 %)	0.2871
	Absent (n = 91)	15 (16.85 %)	6 (6.74 %)	5 (5.62 %)	4 (4.49 %)	59 (66.29 %)	
RDW	Present (n =24)	3 (12.50 %)	0 (0.00 %)	4 (16.67 %)	0 (0.00 %)	17 (70.83 %)	0.1179
	Absent (n = 133)	24 (18.05 %)	8 (6.02 %)	5 (3.76 %)	6 (4.51 %)	90 (67.67 %)	

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; PLT: Platelet; HB: Hemoglobin; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; PCV: Packed Cell Volume; RDW-CV: Red Cell Distribution Width –Coefficient of Variation; CD4 – Cluster of Differentiation 4

4.7 Discussion

Our study findings reported that cytopenias (anaemia, leucopenia and thrombocytopenia) were common haematological abnormalities in both ART – treated and ART – naïve HIV infected patients attending Thika Level Five Hospital CCC, Kiambu County. This study finding is in agreement with Ashenafi et al., (2023). The present study findings indicate that leucopenia was the most common haematological abnormality among the study participants followed by anemia and thrombocytopenia with an overall frequency of 18.9%, 15.2% and 2.5% respectively. Our study findings agree with those of previous studies that reported the most common haematological abnormality was leucopenia (Fan et al., 2020; Kathuria et al., 2016; Akinbami et al., 2010). However, our findings differ with other studies that reported the most common haematological abnormality in HIV infected patients was anemia (Tamir et al., 2019; Assefa et al., 2015).

The overall prevalence of leucopenia in this study was 18.9%, which is lower than 22% reported in India (Kaur et al., 2017) and higher than 13% reported in Ethiopia (Fekene et al., 2018). In the present study, prevalence of leucopenia varied among ART – naïve and ART – treated patients, with a prevalence of 49.0% and 8.5% respectively. The present study findings agree with those of Mathews et al (2013) who found a higher prevalence of leucopenia 8.14% in ART – naïve patients than 3.96% in ART- treated patients. On the contrary, other previous studies have reported a higher prevalence of leucopenia in ART – treated patients than in ART – naïve patients (Thulasi et al, 2016; Enawgaw et al., 2014). However, a prevalence of 49.0% in ART – naïve patients reported in this study is higher than 24.4% reported in Ethiopia (Tamir et al., 2019) and 23.95% reported in India ((Kaur et al., 2017). In the present study, the prevalence of leucopenia in ART – treated patients was 8.5% which is in agreement with another study conducted in Nigeria which reported a leucopenia prevalence of 9% (Sale et al., 2018). However, the prevalence was lower than a 20%

prevalence of leucopenia in ART – treated patients reported in Cameroon (Ako et al., 2018), 35.9% reported by Enawgaw et al (2014) in Gonder, Ethiopia and 35% reported in India by Kumar et al (2016) but higher than 6.5% reported by Afari and Blay (2018) in Ghana and 3% in India by Mitra et al (2015). These observed differences could be due to differences in the study populations, varying clinical characteristics of the study participants and use of different cut – offs for leucopenia.

Prevalence of Leukocytosis in HIV infected patients was found to be 1.3% but it varied among ART – naïve and ART – treated patients with a prevalence of 3.9% in ART – naïve patients and 0.94% in ART – treated patients. The present study findings are in accordance to those of Mathews et al who reported a higher prevalence of leucocytosis in ART – naïve 12.79% than 6.93% in ART – treated patients (Mathews et al., 2013). However, the 3.9% prevalence in ART – naïve patients reported in this study is higher than 2.5% reported in a previous study conducted in Patiala, India (Kaur et al., 2017) but lower than 12.79% reported in New, Delhi, India (Mathews et al., 2013). Similarly, the 0.94% prevalence of leucocytosis among ART – treated patients is lower than 6.93% reported in ART – naïve patients by Mathews et al (2013).

The overall prevalence of lymphopenia in the present study was 7.6% which is lower than 5% reported in Ethiopia (Fekene et al., 2018). Lymphopenia prevalence in the present study varied among the ART – treated and ART – naïve patients with a prevalence of 3.8% and 23.6% respectively. The findings of the present study are in accordance with those of Kaur et al (2017) who reported a higher prevalence of lymphopenia in ART – naïve patients than in ART – treated patients. In our study, the prevalence of lymphopenia of 3.8% in ART – treated patients was higher than 3.6% reported in Goba, Ethiopia (Duguma et al., 2021) but lower than 10.7% prevalence reported by Kaur et al (2017) in India, while a lymphopenia prevalence of 23.6% among ART – naïve patients reported in this study is higher than 2.9% reported among ART- treated patients in Goba, Ethiopia (Duguma et al., 2021) but lower than 32.3% reported among ART – naïve patients by Kaur et al (2017) in India. In the present study, a 0.94% prevalence of lymphocytosis was reported among the ART – treated patients. The possible explanation for these differences could be due to the variation in the study populations, variation in the cut -offs for lymphocytosis, inclusion criteria and the clinical conditions of the study subjects. There was no any case of lymphocytosis in ART – naïve patients.

In the present study the overall prevalence of neutropenia was found to be 12.23% but it varied among ART – treated patients and ART – naïve patients with a prevalence of 15.1% and 17.6% respectively. The high prevalence of neutropenia seen in ART – naïve patients could be attributable to the untreated HIV infection. Infection with HIV virus itself suppresses the bone marrow and leads to decreased levels of granulocyte colony-stimulating factor, and also affects the granulocyte-macrophage lineage, thus resulting in leukopenia and neutropenia (Adane et al., 2012). A 17.6% prevalence of neutropenia in ART – naïve patients reported in our study is higher than 11.4% reported among ART – naïve patients in a previous study conducted in Patiala, India (Kaur et al 2017) and 14.5% prevalence reported in Ethiopia (Enawgaw et al., 2014). Similarly, 15.1% prevalence of neutropenia among ART – treated patients reported in this study is lower than 28.3% prevalence reported by Enawgaw et al (2014) in Ethiopia and slightly higher than 14.4% prevalence of neutropenia reported in Patiala India (Kaur et al 2017). These differences may be due to the variation in study design methods, study populations and clinical conditions of the patients.

The total prevalence of thrombocytopenia was 2.53% but it varied among ART – treated and ART – naïve patients with a prevalence of 0.94% and 7.84% respectively. The present study findings are in accordance with those of Kaur et al (2017) who reported a higher prevalence of 21.87% of thrombocytopenia in ART – naïve than 12.5% in ART – treated patients (Kaur et al., 2017). Prevalence of 0.94% in ART – treated patients reported in the present study is lower than 4.1% reported in HAART – treated patients in Ethiopia (Enawgaw et al., 2014), 4.5% in ART – treated patients reported by Duguma et al (2021) in Gondar, Ethiopia, 11.1% reported by Fekene et al (2018) in Ethiopia and 3% reported by Thulasi et al (2016) in India. Additionally, prevalence of 7.84% in ART – naïve patients reported in the present study is higher than 4.65% reported in New Delhi, India by Mathews et al (2013), 4.5% reported in China (Fan et al., 2015) and 1.6% prevalence in HAART naïve HIV patients recently reported in another study in China (Fan et al., 2020). But it is lower than 8.3% reported among HAART naïve patients in Uganda, 9.0% reported by Enawgaw et al (2014) in Ethiopia, 1.4% reported among ART – naïve patients in Goba Ethiopia by Duguma et al (2021), 18.7% reported in ART- naive HIV positive patients in Dessie, Ethiopia (Tamir et al., 2019). Going by these findings, the prevalence of thrombocytopenia seems to be a bit higher in developing countries than in the developed countries.

In the present study, the total prevalence of anaemia was found to be 15.2% with a higher prevalence of 39.3% in ART – naïve than 15.1% prevalence in ART – treated patients. The present study findings are in agreement with other previous studies which reported a higher prevalence of anaemia in ART –naïve than in ART – treated patients (Kaur et al., 2017; Thulasi et al., 2016; Mathews et al., 2013), The possible explanation for the decreased prevalence of anemia in ART – treated HIV patients seen in our study is probably due to restoration of haemopoiesis in the bone marrow after the initiation of antiretroviral therapy. It has been reported that the decreased in the prevalence of anemia after HAART initiation is due to the positive effect of the treatment on the differentiation and survival of RBCs, viral load suppression, and reduction in the frequency of OIs (Fokouo et al., 2015; Denue, et al., 2013). The anaemia prevalence of 39.32% in ART – naïve patients reported in the present study is higher than 29.7% reported in Gondar, Northwest Ethiopia (Enawgaw et al., 2014), 31.8%, reported by Duguma et al (2021) in Ethiopia and 36.6% reported in antiretroviral-naive adult HIV-infected Patients in Mehal Meda hospital Ethiopia (Fiseha and Ebrahim, 2022) and 9.8% reported in china (Dai et al., 2017). But it is lower than 45.3% reported in New Delhi India (Mathews et al, 2013), 82% reported in India by Thulasi et al (2016) and 89.5% reported in Patiala India (Kaur et al., 2017). In the present study, 15.1% prevalence of anaemia in ART – treated patients was lower than 23.2% reported in North Shewa Zone, Ethiopia (Gebreweld et al., 2020), 24.3% reported in Northeastern Nigeria (Denue et al., 2013) and 23% reported in Kaduna State, Nigeria (Sale et al., 2018). However, it was higher than 3.0% reported in Korea (Choi et al., 2011) and 11.7% reported by Enawgaw et al (2014) in Ethiopia, 11.4% at Black Lion Specialized Hospital, Addis Ababa, Ethiopia (Woldeamanuel et al., 2018) and 14.6% reported in Southeast Ethiopia (Duguma et al 2021). This demonstrates that the prevalence of anaemia is higher in treatment – naïve patients than in ART – treated patients. Findings of this study support that the haematological abnormalities are corrected by initiation of combined antiretroviral therapy by lowering the viral load and the risk of opportunistic infections. In addition, the wide varying differences in prevalence could be due to differences in geographic locations, race and ethnicity, difference in study populations, different criteria used to define anemia and ART status across the studies.

The mean blood cell counts of PLT, ALC, HB, MCV, MCH and PCV of ART – treated was significantly higher compared with mean blood cell counts of ART – naïve HIV infected patients.

The present study findings are in agreement with those of Ashenafi et al., 2023; Kaur et al., 2017; Parinitha et al., 2012. However, the mean ± SD of WBC, ANC and RDW were significantly higher in ART- naïve than in ART- treated HIV patients. This study finding align with those of Tihalun et al (2022) and Kaur et al (2017. The mean CD4 count of ART – treated was higher compared to mean CD4 count of ART – naïve but not significantly different.

The 5 ART regimens AZT/3TC/ATV/r, TDF/3TC/DTG, TDF/3TC/ATV/r, ABC/3TC/ATV/r, and AZT/3TC/DTG used by the HIV – infected patients in this study did not influence the WBC, RBC, PLT, ANC, AMC and HB abnormalities p- value = 0.2475, 0.5214, 0.0800, 0.7537, >0.9999 and 0.8660 respectively. However, the ART regimen significantly influenced the ALC, PCV, MCV, MCH, RDW and CD4 count abnormalities of the ART – treated HIV infected patients (p- value < 0.05). ART – treated patients who were on TDF/3TC/DTG had significantly higher cases of lymphopenia than those on AZT/3TC/ATV/r and ABC/3TC/ATV/r regimens (P = 0.0252). There was no any case of lymphopenia in those taking TDF/3TC/ATV/r, and AZT/3TC/DTG. Thus DTG significantly influenced lymphopenia in the ART – treated patients than abacavir (ABC). There was no available data to compare with due to the variation of ART regimens used in different study populations. In the present study, the ART regimens significantly influenced the PCV abnormalities of the ART – treated HIV infected patients with those on AZT/3TC/ATV/r showing significantly higher 12 (100.00 %) cases of low PCV (P = <0.0001) than those on TDF/3TC/DTG, TDF/3TC/ATV/r, ABC/3TC/ATV/r. There was no any case of low PCV in HIV – patients receiving the other ART regimens. Haematocrit (HCT) is the proportion of whole blood occupied by red cells and hematocrit being a function of the number, volume and blood level of erythrocytes is also used in evaluation of anemia. The present study did not find a significant association between ART regimen and anaemia which is in agreement with other studies (Assefa et al., 2015; Renner et al., 2013; Kiragga et al., 2010). On the contrary, several studies have reported that HIV infected patients developed AZT –induced anemia after treatment with AZT- containing ART regimens (Ikunaiye et al., 2018; Dash et al., 2015; Kuwalairat & Winit-Watjana, 2014). This is because ZDV is mainly associated with myelotoxicity possibly by inhibiting erythroid precursor cells in the bone marrow leading to decreased RBC production manifesting in anemia (Marchionatti & Parisi, 2021; Berhane et al., 2020; Agarwal et al., 2010). However, the present study findings are in contrast with the findings of Echefu et al (2023) who reported that TDF/3TC/EFV, TDF/3TC/LPV/R and TDF/3TC/DTG revealed comparable packed cell volume (PCV) and Hb levels. These differences could be due to the use of different ART drugs combinations in the study subjects. The present study findings indicate that the ART regimen significantly influenced the MCV abnormality (p – value <0.0001) with macrocytosis being significantly higher in those who were on AZT – containing drugs, that is, AZT/3TC/ATV/r and AZT/3TC/DTG with a frequency of 9 (52.94 %) 2 (11.76 %) respectively. Long-term therapy with AZT-containing regimen is reportedly associated with macrocytic anemia, which is related to vitamin B12 and folate deficiency (Parkes-Ratanshi et al., 2015). Zidovudine is a thymidine analog that causes macrocytic anemia by interfering with DNA synthesis (Barik S, 2016). Tadele et al (2014) reported there was a high prevalence of macrocytic anemia (80.6%) after six months of treatment with zidovudine containing ART – regimens, zidovudine- based regimens are responsible for the development of macrocytosis associated with bone marrow toxicity (Tadele et al.,2014). Most of the ART - treated patients 32 (94.12 %) who had hypochromia were on TDF/3TC/DTG and the difference was statistically significant. Most of the ART – treated patients had a normal RDW however most of those who had a high RDW were on TDF/3TC/DTG. There was no available data for comparison. The ART regimen significantly influenced the CD4 count abnormality (P - value - <0.0001). The present study findings are in accordance with those of Echefu et al (2023) who reported a significant difference in the CD4 count of the ART – treated patients between the ART regimens TDF/3TC/EFV, TDF/3TC/LPV/R and TDF/3TC/DTG (p – value = 0.035). In the present study, most of the patients 36 (81.82 %) on Dolutegravir (DTG) had a significantly higher CD4 count of greater than 500 cells/μL of blood than those on atazanavir/ritonavir (ATV/r) and zidovudine (AZT) though the results are from a small sample size. This study finding is in agreement with those of Gebremedhin et al (2024) who reported that The CD4+ T-cell count showed a significant rise in patients undergoing dolutegravir (DTG)-based treatment, suggesting a recovery of cellular immunity.

Patient gender had significant influence on the HB and MCH abnormality, with females having a significantly higher HB abnormality, that is, low HB (p-value = 0.0021) and MCH abnormality, that is low MCH (p-value = 0.0050) than the males. The present study findings agree with other previous studies that have reported significantly lower HB and MCH in female HIV-positive subjects compared with their male counterpart (Ngwu and Eneh 2022; Jacob, 2017; Wankah et al, 2014). Similarly, Duguma et al (2021) reported that anaemia was significantly associated with female HIV infected patients and that female HIV-positive individuals had 2.6 (p = 0.048) times more likely to develop anemia than male individuals. Similar to the findings of a study conducted in Goba, Ethiopia the present study did not report a statistically significant association between patient gender and WBC, PLT, RBC, ANC and ALC abnormality (Duguma et al., 2021).

In the present study, we did not find a significant association between the WBC, RBC, ANC, HB, MCV, MCH and RDW-CV AND patient age groups 18-25years, 26-35years, 36-45 years, 46-55 years, 56-65 years and >66 years (p-value > 0.05). Similarly, a study conducted among ART – treated subjects in Nigeria did not find a significant difference in the mean values of HB, PCV, RBC, MCH, MCV of HIV subjects that are on ART and are within age ranges of 15-30 years, 31-45 years and 46-60 years (P>0.05). Though our study did not find a significant influence of patient age on leucopenia, it contrasts the findings of other studies that reported leukopenia were significantly increased as the age of HIV infected patients increased (Gebreweld et al., 2020; Fekene et al., 2018; Enawgaw et al 2014; Kyeyune et al., 2014). The findings of the present study indicate that patient age significantly influenced the PLT abnormality (p-value = 0.003) with subjects aged 18 – 25 years being more prone to the PLT abnormality 19 (51.35 %) than the other age groups. These findings agree with those of Gebreweld et al (2020) that reported thrombocytopenia was associated with age group however in their study thrombocytopenia was independently associated with age group 40–49 years (PR = 0.33, 95% CI: 0.16–0.70, P = 0.004).

In the present study, marital status significantly influenced the ANC abnormality of the study subjects p-value = 0.0004). There was no available data for comparison.

The present study findings showed that patient BMI significantly influenced the WBC abnormality, that is, leucopenia (p-value = 0.0223). This is in agreement with findings of a study conducted among HIV infected adults in Mehal Meda Hospital, Central Ethiopia that reported that low BMI was significantly associated with presence of any form of cytopenia (leucopenia, anemia and thrombocytopenia) (Fiseha and Ebrahim, 2022)

The findings from the present study demonstrated that use of cotrimoxazole significantly influenced the RBC abnormality of the study subjects (p-value = 0.0262) with those not on cotrimoxazole use being more prone to anaemia. Our findings are in contrast with those of others, who have reported that use of cotrimoxazole prophylaxis is positively associated with development of anaemia (Berhane, et al., 2020; Fekene et al., 2018). Moreover, other studies have reported a negative association between use of cotrimoxazole and prevalence of anemia (Dryden-Peterson et al., 2013). In our study cotrimoxazole use did not significantly influence leucopenia which is in contrast with the findings of fekene et al (2018) who reported that use of co-trimoxazole prophylaxis therapy is positively associated with prevalence of leucopenia. There is need for future large scale studies that are longitudinal in design to be conducted to study the association between cotrimoxazole use and anemia, leucopenia and thrombocytopenia in order to clear this controversy.

ART duration significantly influenced the WBC abnormality and ALC abnormality of the study subjects with those on ART duration of 16 -20 years being more prone to WBC abnormality 4 (40.00 %) and those on 11-15 Years being more significantly affected (76.47 %) by ALC abnormality. This could be due to the long-term exposure myelosupprssive effects of zidovudine since a number of ART –treated patients in our study were on zidovudine containing ART regimens. On the contrary to other hematological abnormalities, it has been reported that the prevalence of leukopenia, neutropenia, and lymphopenia show an increasing pattern after initiation of HAART (Duguma et al., 2021; Kathuria et al.,2016; Afari and Blay, 2018; Ferede & Wondimeneh, 2013; Wisaksana et al., 2013). Long-term ART therapy with zidovudine containing ART regimens causes leukopenia by myelosuppressin in myeloid and erythroid precursors and cytotoxicity of T-cells eventually decreasing the survival of T-cells (Servais et al., 2001; Kaweme et al., 2022). ART duration significantly influenced the PCV abnormality of the study subjects (p-value = 0.0310) with those on a short ART duration of 6 – 10 years being more significantly affected (71.43 %) than those on longer duration of 11-15 years and16 -20 years. This could be due to the haemopoietic recovery that occurs after a period of ART (Choi et al., 2011).

The present study findings indicate that CD4 count (HIV disease stage) significantly influenced the PLT abnormality (p value = 0.0012) of the study subjects with those having CD4 count between 200-499 cells/μL (stage II) being significantly affected (51.35 %) by the thrombocytopenia than those having CD4 count >500cells/μL (stage I) (48.65 %). These study findings agree with those of Enawgaw et al (2014) that reported that thrombocytopenia increases as CD4 count decreases (p = 0.007). Similarly, it has previously been reported that the prevalence of thrombocytopenia is higher in patients with low CD4 cell levels (Thulasi et al., 2016). Further, our study results demonstrate that none of the patients with CD4 count >500cells/μL (stage I) had anaemia.

Our study results demonstrate that Covid -19 vaccine type significantly influenced PLT abnormality (p value = 0.0401) and ANC abnormality (p value = 0.0010) with Non Covid – 19 vaccinated HIV – infected patients having significantly higher PLT abnormality and ANC abnormality than the Covid – 19 vaccinated HIV –infected patients. There was no available data from other studies to compare with our findings. In addition, those on Johnson & Johnson had significantly higher PLT and ANC abnormality than those on Astrazeneca, Moderna and Pfizer while those on Moderna were least affected by both PLT and ANC abnormality. From our study results it is evident that majority of the study subjects who were affected by the haematological abnormalities were none vaccinated against SARS-CoV-2 virus. The possible explanation for this could be due to the positive impact of the Covid -19 vaccines against the Sars – Cov Virus and other related viruses thus reducing the occurence of opportunistic infections leading to an improved immune status of the HIV – infected patients and consequently low frequency of PLT and ANC haematological abnormalities observed in the Covid – 19 vaccinated patients than the non – Covid 19 vaccinated patients. However, this finding was not addressed by others therefore there was no available data for comparison.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 Summary

The findings of this study have demonstrated that there is still a significant burden of haematological and immunological abnormalities in both ART – naïve and ART –treated HIV infected adult patients in the developing countries, even in those HIV patients receiving treatment and care at a HIV comprehensive care centre. Better standard of care and management of HIV – infected patients with regular testing of the haematological and immunological abnormalities is paramount to allow earlier detection of haematological and immunological abnormalities with consequent treatment interventions.

Cytopenias (anemia, leucopenia and thrombocytopenia) were noteworthy findings in the present study with leucopenia being the most frequent haematological abnormality among the study subjects, followed by anemia and lastly thrombocytopenia. The frequencies of all forms of cytopenias (anemia, leucopenia and thrombocytopenia) was higher in ART – naïve than in the ART – treated HIV infected patients and controls. Generally, the ART – treated HIV infected patients had higher mean blood cell levels than the ART – naïve HIV infected patients. In addition, most of the blood cell levels for the ART – treated patients were comparable to those of controls. This is a clear indication that the initiation of ART in HIV – infected patients restores haemopoiesis and improves the numbers of various types of blood cells in the peripheral blood. It has been shown that early use of HAART improves the clinical, hematological, and immunological profiles of patients, delays HIV disease progression and improves survival of HIV-positive individuals, which consequently reduces the transmission of HIV virus (Woldeamanuel & Wondimu, 2018; Group, 2017).

This study revealed that the ART regimen significantly influenced the haematological and immunological (CD4 count) abnormalities of HIV infected patients on antiretroviral therapy. Notable in this study, is the significant influence of DTG on lymphopenia and zidovudine (AZT) on macrocytosis. Similar to the present study findings, a previous study reported there was a high prevalence of macrocytic anemia (80.6%) after six months of treatment with zidovudine containing ART – regimens, zidovudine- based regimens are responsible for the development of macrocytosis associated with bone marrow toxicity (Tadele et al.,2014). Additionally, there was a significant difference in the CD4 count of the ART – treated HIV infected patients between the five ART regimens. It is therefore important that a careful choice of the ART regimen for the patient should be made by the clinicians responsible for the ART programme after having considered all the factors necessary. In addition, haematological parameters should regularly be investigated at specified intervals in order to monitor the patient for the development of haematological and immunological abnormalities during antiretroviral treatment which can inform drug discontinuation and drug modification.

This study has revealed the factors that are associated with the haematological (anaemia, leucopenia and thrombocytopenia) and also the association of the immunological CD4 count with the haematological abnormalities. Patient gender, age, marital status, BMI, ART duration, CD4 count, Covid – 19 vaccine type were all positively associated with either of the haematological abnormality. Coinfection with Hepatitis A, B and C was not associated with the haematological abnormalities.

5.2 Conclusions

1. Cytopenias (anaemia, leucopenia and thrombocytopenia) were common haematological abnormalities in both ART – treated and ART – naïve HIV infected patients, with a higher frequency of the abnormalities seen in the ART – naïve HIV infected patients. Leucopenia was the most common haematological abnormality followed by anemia and thrombocytopenia
2. The mean blood cell counts of most of the haematological parameters (PLT count, ALC, HB, MCV, MCH and PCV) of ART – treated was significantly higher compared with mean blood cell counts of ART – naïve HIV infected patients. The mean CD4 count of ART – treated was higher compared to mean CD4 count of ART – naïve but not significantly different.
3. Specific ART regimens had significant influence on haematological abnormalities. The ART regimen significantly influenced the ALC, PCV, MCV, MCH, RDW and CD4 count abnormalities of the ART – treated HIV infected patients. There were significantly higher cases of lymphopenia in TDF/3TC/DTG regimen treated patients while macrocytosis was significantly higher in those who were on AZT/3TC/ATV/r.
4. ART duration influenced haematological abnormalities, with longer durations correlating with specific abnormalities such as leucopoenia, lymphopenia and HCT variations. ART duration significantly influenced leucopenia and lymphopenia of the study subjects.
5. Patient demographics, including gender, age, and marital status, exerted significant impacts on haematological parameters. Females had a significantly higher low HB and low MCH than the males.

6. Low CD4 count was significantly associated with thrombocytopenia underscoring the importance of immune monitoring in managing HIV-related complications.
7. Covid -19 vaccine type significantly influenced PLT abnormality and ANC abnormality. Non Covid – 19 vaccinated HIV – infected patients had significantly higher PLT abnormality and ANC abnormality.

5.3 Recommendations

1. The HIV- infected patients on ART should be regularly monitored for haematological and immnunological abnormalities for prompt detection of development of these abnormalities and consequent treatment and clinical interventions so as to reduce morbidity and mortality. More so, there is need for tailored monitoring and management strategies that consider patient demographics and disease progression.
2. Clinicians responsible for the ART programme at the HIV comprehensive care centres should investigate the haematological and immunological parameters before initiation of ART and consider all the necessary factors before choice of the ART regimen. Clinicians should give more focus to selection of ART regimens that are safer and more individualized for the patient so as to reduce the risk of drug-related hematological toxicities. They should be vigilant about drug interactions and adverse effects.
3. It is important that ART initiation is done early enough so as to reduce the magnitude of haematological and immunological abnormalities in the newly diagnosed ART – naïve HIV infected patients. Therefore, this study recommends that the government of Kenya, through the Ministry of Health (MOH) should come up with strategies and allocate more resources on programmes that support early HIV testing and diagnosis of HIV infection in

the general population so that antiretroviral treatment and care can commence early so as to reduce the burden of these abnormalities.

4. Large scale longitudinal studies are needed so as to understand the long-term effects of ART on haematological parameters. This will enable development of novel interventions to mitigate adverse outcomes, as well as have an in-depth exploration of other haematological (such as coagulation profile abnormalities) and other immunological abnormalities in HIV infected patients and their causes so as to determine the cause effect relationships between the independent variables and the haematological & immunological abnormalities.
5. Basic haematologic tests such as the complete blood count should be used as a screening tool to assess the severity and progression of HIV disease if the viral load and the CD4 count are unavailable especially in the resource limited settings.

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APPENDICES

Appendix I: Informed Consent Explanation and Consent Form for HIV patients

Informed Consent

I, Esther Wangui Mandania, a PhD student at Mount Kenya University is asking you to volunteer for this study to answer questions about HIV and antiretroviral therapy and also provide a total of 5ml blood samples in both EDTA and serum tubes. This informed consent is active and documented. Before you decide to participate in this research, you will be taken through all the elements of the informed consent where all the information about the research will be read and fully explained to you to ensure proper understanding. You are free to interrupt and ask any questions that you may have about the research, which will be answered. Also sufficient time will be given to you to make the decision on whether to participate or not. If there is anything or any word that you do not understand, please ask me to stop as we go through the information and i will take time to explain. If you agree to participate in this study, you will be asked to sign this informed consent form or make your mark in front of a witness and provide 5ml of blood sample in both EDTA and serum tubes. Samples will be collected at three-point time i.e. at diagnosis (month 0), 3 and 6 months. You will also be given a copy of this form.

Purpose of the Research

HIV infection is associated with alteration of hematological and immunological markers. These alterations are linked to disease progression. The antiretroviral therapy (ART) has been associated with improvement and restorations in HIV-associated haematological and immunological abnormalities. The overall aim of this study is therefore to determine the haematological and immuological abnormalities in a cohort of HIV-infected adult Patients at the Thika Level Five Hospital CCC, Kiambu County. The study enrolled a total of 237 study participants who included

ART – naïve & ART - treated HIV positive patients as well as HIV – negative controls into the study.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about the questions you will be asked in this study, it is important that you know the following:

- You do not have to be in this study if you do not want to
- If you choose not to be in this study, it will not affect the care that you receive at your regular facility
- You will be asked to fill in a short questionnaire that will help us collect more data.
- The answers you provide will remain confidential and identifying information about you will not be shared
- You will also be asked to provide blood samples for further analysis

RISKS AND/OR DISCOMFORTS

You may feel embarrassed when talking about your opinions about HIV and your lifestyle. Further, you might feel a little discomfort when blood samples will be drawn from you.

BENEFITS

You may get no direct benefit from answering the questions or by providing your samples.

Having your hematological, immunological and viral loads levels monitored will be vital in helping your clinician provide better personalized management. Your participation in the study will be key in contributing to our understanding about ART treatment outcomes

COSTS TO YOU

There is no cost to you for the answering the questions.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. Any information about you will be identified only by code and not by name

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, you should contact Esther Wangui Mandania 0727906351/0751187115

If you have questions about your rights as a research participant, you should contact the Secretary of the Mount Kenya Kenya University Ethics Review Committee, P. O. Box 342-01000, Thika. Telephone number: 0709 153 000**;** (+254 20) 2088310; Email: cgsr@mku.ac.ke

STATEMENT OF CONSENT AND SIGNATURES

I have read this consent form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in this study is voluntary. I understand that if i decide to answer the questions, i may withdraw at any time. By signing this form, i do not give up any rights that i have as a research participant.

______________________	______________________	______________
Participant Name (print)	Participant Signature/Thumbprint	Date
______________________	______________________	______________
Study Staff Conducting Consent (print)	Study Staff Signature	Date
______________________	______________________	______________
Witness Name (print)	Witness Signature	Date

Appendix II: Consent Form /questionnaire for Blood Donors

CONSENT/QUESTIONAIRE FOR RESEARCH PURPOSES.

STUDY TITLE: HAEMATOLOGICAL AND IMMUNOLOGICAL ABNORMALITIES IN HIV INFECTED ADULT PATIENTS AT THIKA LEVEL FIVE HOSPITAL COMPREHENSIVE CARE CENTRE, KIAMBU COUNTY, KENYA.

I, Esther Wangui, the principal investigator, hereby request your participation in the above mentioned proposed study. Therefore, you are requested to grant permission for the use of your blood specimen for the purposes of the proposed study. Before you decide to participate in this study, all the information about the research study will be fully explained to you to ensure proper understanding. If you agree to participate in this study, you will be asked to provide your demographic information by filling this form and provide 5ml of venous blood sample in EDTA tube.

Please sign the consent statement below as an indication that you have granted permission for your blood specimen to be used for the proposed study.

(Please fill in where appropriate)

(1) Study number: …………………………………………Date: ………………………

(2) Contact: Mobile Phone number: ………………………..P.O.Box:…………………

(3) Gender (tick): ☐ Male ☐ Female

(4) Age: ……………. (Years)

(5) Weight …………. (Kg)

(6) Height…………… (Metres)

(7) BMI………………………………..

(8) Occupation………………………………………..

(9) County……………………………………………

(10) Are you on any medication (tick): YES/NO

If YES, please specify: ……………………………………………………….

I………………………………… (Study Number), have been given all the information about the proposed study and have given consent for my blood to be used ONLY for the proposed study indicated above.

Signature……………………………………Date: ………………………………………

Appendix III: Questionnaire for HIV patients

Questionnaire for Research Purposes

STUDY TITLE: HAEMATOLOGICAL AND IMMUNOLOGICAL ABNORMALITIES IN HIV INFECTED ADULT PATIENTS AT THIKA LEVEL FIVE HOSPITAL COMPREHENSIVE CARE CENTRE, KIAMBU COUNTY, KENYA.

I am Esther Wangui Mandania, a PhD student at Mount Kenya University Department of Medical Laboratory Sciences, Medical School. I am conducting research on haematological and immunological abnormalities of HIV Infected Patients Attending Thika Level Five Hospital Comprehensive Care Clinic.

This is a structured questionnaire that is intended to provide the researcher with important information regarding haematological and immunological changes in HIV – positive patients who are taking antiretroviral therapy in order to evaluate the effects of ART on these parameters and the role ART plays in the amelioration of these haematological abnormalities.

Kindly provide the researcher with the following information;

A1: INTERVIEW INFORMATION

A1.2: Interview ID No/Study No…………………………………………………

A1.3: Date of Interview DD/MM/YY…………………………………

A1.4: Time of the Interview……………………………………………..

SOCIO DEMOGRAPHICS

A2.1: Sex of the Respondent

□ Female

□ Male

A2.2: How Old Are You? ……………………………………….

A2.3: What is your residence?...

A2.4: what is your contact information?

□ Mobile Phone Number…………………………………………………

□ Postal Address………………………………………………………..

□ Email (if available)………………………………………………….

A2.5: What was the last level of school you completed?

□ No formal education…………………………………………………

□ Primary……………………………………………………………..

□ Secondary……………………………………………………

□ Post -Secondary………………………………………………………

□ Other - Specify…………………………………………………………..

A2.6: What is your occupation/What kind of work do you do?..................................

A2.7: During the past month, how often did you have challenges getting the food that you need?

□ Never…………………………………………………

□ Sometimes…………………………………………………………..

□ Often…………………………………………………

□ Always…………………………………………………

A2.8: Please tell me about the problems……………………………..................................

………………………………………………………………………………………

A2.9: What is your marital status?

□ Single…………………………………………………

□ Married or cohabiting…………………………………………………………..

□ Divorced or separated………………………………………………………

□ Widowed………………………………………………………

□ Other -specify………………………………………………………

A3.0: What is your height, weight and BMI (to be calculated)

□ Weight in Kg………………………………………………………

□ Height in meters…………………………………………………………..

□ BMI………………………………………………………

ART REGIMENS AND ACCESS

B 3.1: When did you test positive for HIV?

Record date…………………………………………………………………………

B3.2: When did you start taking ARV drugs?

Record date………………………………………………………………………….

B3.3: Which ARV regimen are you taking?

(Confirm from records) …………………………………………………………………

B3.4: In the past one month, have you had problems getting your ART?

□ Yes………………………………………………………

□ No…………………………………………………………..

□ Don't remember………………………………………………………

B3.5: Please tell me about the problem……………………………………

………………………………………………………………………………………………..

HEALTH STATUS

B4.0: How would you rate your health before you started taking ART?

□ Excellent……………………………………………………

□ Very Good……………………………………………………..

□ Good……………………………………………………………..

□ Fair…………………………………………………………………

□ Poor…………………………………………………………………

B4.1: Now that you are taking ART, how would you rate your current health status?

□ Excellent……………………………………………………

□ Very Good……………………………………………………..

□ Good……………………………………………………………..

□ Fair…………………………………………………………………

□ Poor…………………………………………………………………

B4.2: Do you suffer from any chronic illness?

□ Yes…………………………………………………

□ No…………………………………………………………..

B4.3: If yes, which chronic illness?..

…………………………………………………………………………………………………

ART SIDE EFFECTS

B4.2: Since you started taking ART, have you experienced any side effects or body changes?

□ Yes…………………………………………………

□ No…………………………………………………………..

□ Don't know…………………………………………………

B4.2: Please tell me more about these side effects or body changes that you have experienced…

………………………………………………………………………………………………...

……………………………………………………………………………………………………

B4.3: What is the prescribed dose of all the ART medications that you take (obtain information from the patient or health care provider)

Name of medication	**Morning dose (no of pills)**	**Morning dose (no of pills)**	**Morning dose (no of pills)**	**Daily total no of pills**
1.				
2.				
3.				

ART ADHERENCE AND INTERRUPTIONS OVER THE PAST ONE MONTH

B5.1: Have you missed taking any of your prescribed medications in the past month?

□ Yes…………………………………………………

□ No……………………………………………………..

B5.2: Which type of medication did you not take or missed taking?..................................

(Refer to the above table in B5.1 for the type of ART medication)

Missed dose #1... ....

Missed dose #2 ....

Missed dose #3 ....

B5.3: How many times did you miss taking the dose of your medication?

Missed dose #1... ....

Missed dose #2 ....

Missed dose #3 ....

B5.4: During the last month, did you ever stop taking your ART medication for 48hrs or longer?

□ Yes…………………………………………………

□ No……………………………………………………..

B5.5: What step did you take when you realized you have missed taking your ART medication as prescribed?..

……………………………………………………………………………………………………..

B5.6: For how long did you stop taking your ART for 48hrs or longer?

□ More than 48hrs……………………………………………………………………

□ One week……………………………………………………………………

□ Two weeks…………………………………………………………………....

□ Three weeks………………………………………………………………….

□ One month……………………………………………………………………

B5.7: What were the reasons why you stopped taking ART?..

……………………………………………………………………………………………

CONCURRENT MEDICATION

B6.1: Are you taking any other drugs prescribed by your clinician?

□ Yes…………………………………………………

□ No……………………………………………………..

B6.2: If yes, which drugs are you taking?...

…………………………………………………………………………………………………

B6.3: What illness are the drugs you are taking treating?...

……………………………………………………………………………………………………

B6.4: Are there other drugs you are taking which have not been prescribed by your clinician?

□ Yes…………………………………………………

□ No……………………………………………………..

B6.5: If yes, which drugs?..

………………………………………………………………………………………………………

B6.6: What illness are the drugs you are taking treating?..

B6.7: During the last month, have you visited the hospital or sought the services of a healthcare provider because of any illness?

□ Yes…………………………………………………

□ No……………………………………………………..

B6.8: If yes, Please tell me more about the illness and the treatment that was given to you?

……………………………………………………………………………………………….

………………………………………………………………………………………………

DRUG AND ALCOHOL USE

B7.1: During the past month, how often have you taken alcohol or any alcoholic drink?

□ Daily………………………………………………………………………..

□ Almost every day……………………………………………………………

□ 3-4 times a week…………………………………………………………….

□Once or twice a week …………………………………………………………

□ 1-3 times a week ……………………………………………………………

□ Never……………………………………………………………………….

B7.1: During the past month when you drunk alcohol, how many bottles or glasss of the alcoholic drink did you take at ago?

□ 1-2 drinks per day……………………………………………………………

□ 3-5 drinks per day …………………………………………………………

□ 6 or more drinks per day ………………………………………………..

B7.3: During the past month, have you used non – prescribed drugs such as injectable drugs?

□ Yes…………………………………………………

□ No……………………………………………………..

B7.4: If yes, which drugs have you used?..

……………………………………………………………………………………………………

Appendix IV: ERC Approval

Mount Kenya University

REF: **MKU/ERC/1940**

Date: 29 September 2021

TO: **ESTHER WANGUI MANDANIA**

REG: **PHDMLS/2020/66736**

Dear Sir/Madam,

RE: EFFECTS OF ANTIRETROVIRAL THERAPY ON HAEMOPOIETIC GROWTH FACTORS AND IMMUNOLOGICAL PARAMETERS OF HIV-1 INFECTED PATIENTS ATTENDING THIKA COMPREHENSIVE CARE CLINIC

This is to inform you that **Mount Kenya University** has reviewed and approved your above research proposal. Your application approval number is **1013.** The approval period is **29/09/2021 - 28/09/2022.**

This approval is subject to compliance with the following requirements;

i. Only approved documents including informed consents, study instruments, MTA will be used

ii. All changes including amendments, deviations and violations are submitted for review and approval by **Mount Kenya University**

iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to **Mount Kenya University** within 72 hours of notification

iv. Any changes, anticipated or otherwise that may increase the risks or affect the safety or welfare of study participants and others or affect the integrity of the research must be reported to **Mount Kenya University** within 72 hours

v. Clearance for export of biological specimens must be obtained from relevant institutions

vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal

vii. Submission of an executive summary report within 90 days upon completion of the study to **Mount Kenya University**

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

The Chairman
Mount Kenya University
Ethics Review Committee
P. O. Box 342 - 0100, Thika

Yours sincerely,

Dr. Peter G. Kirira
Chairman, Mount Kenya University IERC

Main Campus, General Kago Road, P.O. Box 342-01000 Thika. Tel: +254 67 2820 000,

Appendix V: Introductory Letter

Mount Kenya University

DIRECTORATE OF GRADUATE STUDIES

PHDMLS/2020/66736

27th October, 2021

The Director, Research Coordination Division
National Commission for Science, Technology & Innovation
Utalii House, 8th & 9th Floor
P.O Box 30623- 00100
NAIROBI

Dear Sir/Madam,

RE: ESTHER WANGUI MANDANIA – REGISTRATION NO. PHDMLS/2020/66736

The purpose of this letter is to introduce the above named student who is pursuing **Doctor of Philosophy in Medical Laboratory Sciences** in the **Department of Medical Laboratory Sciences** in the **Medical School.**

The title of her research is ***"Effects of Antiretroviral Therapy on Haemopoietic Growth Factors and Immunological Parameters of HIV-1 Infected Patients Attending Thika Comprehensive Care Clinic."***

She has been cleared by the University's Ethics Review Committee (Certificate attached) and now has to proceed to the field to collect data for her research between **November and April, 2022.**

Any assistance accorded to her will be highly appreciated.

Thank you.

Mount Kenya University
P. O. Box 342 - 01000, THIKA
Office of the Director
Graduate Studies

Dr. Samuel M. Karenga, Ph.D
Director, Graduate Studies
Enc.

Main Campus, General Kago Road, P.O. Box 342-01000 Thika. Tel: +254 67 2820 000,
Cell: +254 720 790 796, 0709 153 000
Email:info@mku.ac.ke, Web: www.mku.ac.ke
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Appendix VI: NACOSTI Approval

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **899589**

Date of Issue: **26/November/2021**

RESEARCH LICENSE

This is to Certify that Ms.. ESTHER WANGUI MANDANIA of Mount Kenya University, has been licensed to conduct research in Kiambu, Nairobi on the topic: EFFECTS OF ANTIRETROVIRAL THERAPY ON HAEMOPOIETIC GROWTH FACTORS AND IMMUNOLOGICAL PARAMETERS OF HIV-1 INFECTED PATIENTS ATTENDING THIKA COMPREHENSIVE CARE CLINIC for the period ending : 26/November/2022.

License No: **NACOSTI/P/21/14506**

899589

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

Appendix VII: Kiambu County Approval

COUNTY GOVERNMENT OF KIAMBU
DEPARTMENT OF HEALTH SERVICES

All correspondence should be addressed to HEAD
HRDU – HEALTH DEPARTMENT
Email address: mndiritu@gmail.com
mkwasa@live.com
Tel. Nos: 0721641516
0721974633

HEALTH RESEARCH AND DEVELOPMENT UNIT
P. O. BOX 2344 – 00900
KIAMBU

Ref. No.: KIAMBU/HRDU/22/03/09/RA_MANDANIA   Date: 09th Mar 2022

TO WHOM IT MAY CONCERN

RE: CLEARANCE TO CONDUCT RESEARCH IN KIAMBU COUNTY

Kindly note that we have received a request from Ms. Esther Wangui Mandania of Mount Kenya University to carry out her study in Kiambu County, the research topic being on "**Effects Of Antiretroviral Therapy On Haemopoietic Growth Factors And Immunological Parameters Of HIV-1 Infected Patients Attending Thika Comprehensive Care Clinic**"

We have duly inspected her documents and found that she has been cleared by NACOSTI to carry out the research for a period ending **26th November 2022**. She thus does not need any further clearance with another regulatory body in order to conduct research within the county of Kiambu.

However, it is incumbent upon the institution where she is carrying out research to ensure that she receives adequate supervision during the process of conducting the research. This note also accords her the duty to provide a feedback on her research to the county at the conclusion of her research.

DR. MWANCHA KWASA
COUNTY CLINICAL RESEARCH OFFICER
KIAMBU COUNTY

Appendix VIII: Data Collection Approval

MINISTRY OF HEALTH

OFFICE OF THE DIRECTOR GENERAL

Telephone: Nairobi 254-020-2717077

Email: dghealth2019@gmail.com

Afya House
Cathedral Road
P.O. Box 30016-00100
NAIROBI

When replying please quote:

REF: MOH/ADM/1/1/82(172)

2nd March, 2022

Ms. Esther Wangui Mandania
Mount Kenya University
P.O BOX 342 – 01000
Thika, Kenya
Mob: 0727906351/0751187115
Email: emandania@yahoo.com, emandania@mku.ac.ke

RE: STUDY AUTHORIZATION AND PERMISSION TO COLLECT BLOOD SAMPLES AT THIKA BLOOD SATELLITE

This is reference to your letter dated 22nd February, 2022 requesting for authorization to conduct a study titled; **"Effects of Antiretroviral Therapy on Hemopoietic Growth Factors and Immunological Parameters of Hiv-1 infected patients attending Thika Comprehensive Care Center".** She is requesting for study authorization and permission to collect comparison blood samples from donors visiting Thika Blood Satellite in Kiambu County.

The study sites will be Thika Level five and Ruiru Sub-district Hospital Comprehensive Care Clinic in Kiambu County.

The purpose of this letter is to inform you that this office has **No Objection** to this study.

You are directed to: -

1. To Collaborate with the Director Health Kiambu County and Head Kenya National Blood Transfusion Service
2. Provide a study progress update every six months until completion of the study using the attached template to dhealthpolicy.research.kenya@gmail.com.

ISO 9001:2015
Certified

3. The first such report is expected on or before 31st September, 2022.
4. Submit the final study report to this office.

Note that this approval applies to this request only.

For Dr. Patrick Amoth, EBS
Ag. DIRECTOR GENERAL FOR HEALTH

CC: Director Health Kiambu County
: Head Kenya National Blood Transfusion Service

ISO 9001:2015 Certified

Appendix IX: Map of the Study Site

Appendix X: Similarity Report

Esther Wangui Mandania

HAEMATOLOGICAL AND IMMUNOLOGICAL ABNORMALITIES IN HIV INFECTED ADULT PATIENTS AT THIKA LEVEL FIVE H...

Quick Submit

Quick Submit

Mount Kenya University

Document Details

Submission ID
trn:oid:::1:3080229780

Submission Date
Nov 15, 2024, 2:27 PM GMT+3

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File Name
ESTHER_WANGUI_MANDANIA_THESIS_FINAL_14-11-24.docx

File Size
11.2 MB

212 Pages

52,941 Words

293,802 Characters

15% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

Filtered from the Report

- Bibliography
- Cited Text

Exclusions

- 1 Excluded Source

Match Groups

- **591** Not Cited or Quoted 15%
  Matches with neither in-text citation nor quotation marks
- **0** Missing Quotations 0%
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- **2** Missing Citation 0%
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Top Sources

0%	Internet sources
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Integrity Flags

1 Integrity Flag for Review

- **Replaced Characters**
  35 suspect characters on 29 pages
  Letters are swapped with similar characters from another alphabet.

Our system's algorithms look deeply at a document for any inconsistencies that would set it apart from a normal submission. If we notice something strange, we flag it for you to review.

A Flag is not necessarily an indicator of a problem. However, we'd recommend you focus your attention there for further review.

Match Groups

- 591 Not Cited or Quoted 13%
  Matches with neither in-text citation nor quotation marks
- 0 Missing Quotations 0%
  Matches that are still very similar to source material
- 2 Missing Citation 0%
  Matches that have quotation marks, but no in-text citation
- 0 Cited and Quoted 0%
  Matches with in-text citation present, but no quotation marks

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0% Internet sources
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The sources with the highest number of matches within the submission. Overlapping sources will not be displayed.

1	Student papers	Far Eastern University	1%
2	Publication	"Encyclopedia of AIDS", Springer Science and Business Media LLC, 2018	1%
3	Publication	Shewaneh Damtie, Lemma Workineh, Teklehaimanot Kiros, Tahir Eyayu, Tegena...	1%
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9	Student papers	Kisii University	0%
10	Student papers	University of Nairobi	0%