HIV INFECTION AS A RISK FACTOR FOR VENOUS THROMBOSIS A CASE-CONTROL STUDY AT KENYATTA NATIONAL HOSPITAL

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I **Dr. Ibrahim .S. Huballah** declare that this research dissertation is my original work and that to the best of my knowledge it has not been presented for the award of a degree at any other university.

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LIST OF ABBREVIATIONS

AIDS:	Acquired Immune Deficiency Syndrome
APC:	Activated Protein C
APL:	Anti-Phospholipid Antibodies
AT-	Anti thrombin
CMV:	Cytomegalovirus
CNS:	Central Nervous System
CTPA:	Computed Tomography Pulmonary Angiogram
DIC:	Disseminated Intravascular Coagulation
DVT:	Deep Venous Thrombosis
FDP:	Fibrinogen Degradation Products
HAART:	Highly Active Anti-Retroviral Therapy
HC II:	Heparin Cofactor II
HIC:	High Income Countries
HIV:	Human Immunodeficiency Virus
IDU:	Injection Drug Users
IL-1:	Interleukin 1
IL-6:	Interleukin 6
IPG:	Impendence Plethysmography
KNH:	Kenyatta National Hospital
KS:	Kaposi Sarcoma
NHL:	Non Hodgkin Lymphoma
OCP:	Oral Contraceptive Pill

PTB:	Pulmonary Tuberculosis
PI:	Principal Investigator
PE:	Pulmonary Embolism
PAI-1:	Plasminogen Activator Inhibitor 1
PTE:	Pulmonary Thromboembolism
PTS:	Post Thrombotic Syndrome
SLE:	Systemic Lupus Erythematosus
SSA:	Sub Sahara Africa
sTM:	Thrombomodulim S
TF:	Tissue Factor
TNF:	Tumor Necrosis Factor
tPA:	Tissue Plasminogen Activator
VCT:	Voluntary Counselling and Testing
V/Q Scan:	Ventilation Perfusion Scan
VTE:	Venous Thromboembolism
vWF:	Von Willebrand Factor

ABSTRACT

Background:

The association between HIV infection and venous thrombosis has long been postulated. It is estimated that HIV infected patients have a 2 to 10 fold increased risk of developing venous thrombosis. However the majority of studies done were retrospective cohort with selection bias and no controls. All the studies were undertaken in first world countries with missing confounding variables. A systematic review by Klein et al of these major studies concluded that there is some evidence linking HIV infection with venous thrombosis but further studies preferably case-control are needed to elucidate this link. Venous thrombosis remains a common cause of morbidity and mortality in both ambulatory and hospitalized patients.

Objective:

To establish if there is an association between venous thrombosis and HIV infection amongst patients at Kenyatta National Hospital

Study Design, Site and Subjects

This was a hospital based case control study at Kenyatta National Hospital. Admitted patients with clinical and doppler evidence of deep venous thrombosis and/or patients with pulmonary embolism confirmed with Computed Tomography Pulmonary Angiogram were defined as a case. Controls were age and sex matched individuals without clinical evidence of deep venous thrombosis and/or pulmonary embolism who seek voluntary HIV testing at the Voluntary Counselling and Testing center in Kenyatta National Hospital within the study period. A case to control ratio of 1:1 was used.

Clinical Method:

Consecutive sampling method of both cases and controls was done. A consent form was issued to the participant for signing after counselling about the study. The data collecting form was filled with the help of the Principal Investigator or research assistant to obtain relevant data for the study controlling for venous thrombosis risk factors. The participant was examined by the principal investigator and pertinent variables such as BMI, HIV status, smoking history, cancer, recent central venous catheterization, recent surgery trauma or immobilization, pregnancy, use of oral contraceptive pills and long distance travelling was noted. Patient confidentiality was maintained throughout this research.

Data Analysis:

The results are presented in the form of tables and charts using SPSS version 21. The association between venous thrombosis and HIV was done using univariate analysis and odds ratio. Multivariate logistic regression analysis was done to determine factors independently associated with venous thrombosis.

Results:

Of the 62 cases of venous thrombosis 23 were HIV positive. Of the 62 controls only 7 were positive for HIV. In a univariate analysis the odds of having venous thrombosis in an HIV positive patient was 4.634 times than that of HIV negative patients (P=0.001, 95% CI 1.810 – 11.866). Controlling for traditional risk factors in a multiple logistic regression model, HIV remained an independent risk for venous thrombosis with an aOR 6.6 (P=0.006, 95% CI 1.7 – 25.6).

Conclusion:

HIV is a risk factor for venous thromboembolism. The odds of venous thrombosis in an HIV infected person is 5 to 7 times higher than the general population.

1.0 CHAPTER ONE:

1.1 Introduction

The relationship between HIV infection and venous thromboembolic disease has long been postulated and remains controversial. HIV infection has evolved into a multisystem chronic infection affecting virtually every organ in the human body. Various studies have been done to elucidate the link between HIV infection and VTE. The majority of the studies done however are retrospective cohort studies in first world cohorts with no controls. These were prone to selection bias with missing confounding variables.

Venous thromboembolic disease can occur in ambulatory patients with AIDS with no other known underlying risk factors {1}. Multiple haematologic and pathophysiological abnormalities responsible for a hypercoagulability state in HIV infected patients have been described. These include deficiencies of antithrombotic proteins (Antithrombin, Protein C, & S, Heparin cofactor 2) and the presence of procoagulant (Antiphospholipid antibodies, Von Willebrand factor). The presence of opportunistic infections and malignancies have also been implicated in the pathophysiological process of venous thromboembolism in HIV infection {1}. Opportunistic infections in these patients increase risk of VTE by lowering Protein S and through immobility {1,2}. The chronic inflammation in patients with HIV increases levels of C4 binding proteins which binds protein S thus decreasing its free circulatory levels.

1.2 Literature Review

1.2.1 Epidemiology of HIV and VTE

HIV remains a global pandemic with an estimated 36.7 million people globally living with HIV at the end of 2015 according to UNAIDS. Of this figure 19 million are in Central and East Africa. Kenya has an average HIV prevalence rate of 6.8% with about 1.6 million people living with HIV infection (National AIDS Control Council 2014). It is one of the six “High Burden” countries in Africa with Swaziland having the highest prevalence. The high burden of HIV and AIDS in Kenya accounts for an estimated 29% annual adult deaths, 20% maternal mortality and 15% deaths in children less than 5 years

VTE remains a common cause of morbidity and mortality {3}. It is the third most common cause of cardiovascular disease after atherosclerotic heart disease and stroke {4}. The true incidence and prevalence of VTE in Kenya remains unknown. As many as 50% of patients with radiologic evidence of venous thrombosis lack specific signs and symptoms {5, 6} which confers its subclinical and inherent accuracy of clinical diagnosis. The most feared

complication of DVT is Pulmonary Embolism (PE). The risk of recurrent DVT and its long term major disability from post Thrombotic Syndrome (PTS) is also of significance {7, 8, 9, 10}.In patients with symptomatic DVT as many as 40% have silent PE {11}. Thirteen percent of patients with DVT and PE demonstrate clinical progression despite full anticoagulation.

VTE is usually more common in individuals > 40 years. Males appear to be at a higher risk in earlier ages than females with a M:F ratio 1.2:1. However the incidence increases 4 folds in the elderly (age > 60 years) in both sexes. In a retrospective study by Copur et al {14} in 2002 in the United States, 362 HIV patients were recruited and an incidence of 2.76% of VTE was found. He concluded that the frequency of VTE among HIV was higher (2.8%) compared to non HIV patients (1.8%). He further concluded that HIV positive patients <50 years of age are at an increased risk for VTE compared with non HIV patients.

Laing et al {15} conducted a retrospective study in 1996 to compare the incidence of DVT in HIV patients and those with full blown AIDS. In a sample size of 728 HIV patients recruited an incidence of 0.96% DVT was observed. However with a review of 250 AIDS patients the incidence was found to be double at 1.60%. He concluded that the risk of VTE in HIV patients is higher as the disease advances.

Saif et al {1} from the National Cancer Institute, National Institute of Health, Maryland in 2001 conducted an initial retrospective study of 131 patients with HIV admitted from January 1993 to January 1998 and found an incidence of 7.63% of VTE. In another study he reviewed 45 patients with HIV who developed venous thromboembolic disease and found a significantly higher incidence of 24% in patients with low CD4 counts (< 200/mm) in comparison to 1.1% in patients with higher CD4 count. Of these patients, 5 had opportunistic infections, 3 had malignancies whilst 2 patients with auto immune haemolytic anemia (AIHA) developed pulmonary embolism following transfusion of red cells. He concluded abnormalities correlate with the degree of immune suppression (CD4<200 cells), presence of concurrent infections and neoplastic disorders. Further studies support his findings and estimate DVT to be ten times more common in HIV and AIDS patients with severe immune suppression {16, 17, 18}.

Saber et al {4} in 2001 did a retrospective study of 4752 patients with HIV recruited from January 1995 to January 2000 in Mount Sinai School of Medicine in New York and found 45 patients had HIV with an incidence of 0.95% of DVT in his sample size. 36 patients were

males, 38 had infectious complications whilst 13 had underlying malignancies. He emphasized on the recommendation of prevention as HIV is a considerable risk factor for DVT.

Sullivan et al {19} in 2000 conducted one of the largest retrospective studies of incidence of DVT in HIV infected patients in the United States. He recruited 42,935 HIV patient records of patients >13 years old from 100 medical clinics in 9 U.S cities. He found an incidence of 2.6% DVT. He concluded that DVT is more common in hospitalized patients with opportunistic infections and in individuals aged >45 years.

A systematic review by Klein et al {20} of 10 of these major epidemiological studies from 1991 to 2004 revealed evidence suggesting that chronic HIV infection is associated with a two to tenfold increased risk of venous thromboembolism in comparison with the general population of the same age. The population sizes in the studies reviewed ranked from 60 to 42,935 with an incidence range of VTE in HIV patients from 0.19% (George et al) {21} to 18% (Hassell et al) {22}. The frequencies of VTE described strongly depend on the patient population being studied and the sensitivity and specificity of the methods used {23}.The conclusion of this major study has been that although evidence pointed towards a relationship between HIV infection and VTE disease, more studies were indicated to further elucidate this link. The majority of studies reporting on documented prothrombotic abnormalities were retrospective studies conducted in first world cohorts with no controls and missing confounding variables. He emphasized on the need of a case-control study.

The increased risk of VTE might require preventive measures in hospitalized patients with HIV, but there are currently no studies to guide clinical practice. With the economic constraints, administering prophylaxis to all patients admitted to hospital with HIV is not cost-effective, especially in low- and middle-income countries {24}.

1.2.2 Pathogenesis and Pathophysiology of Venous Thromboembolism in HIV Infection

Venous thrombosis was first described by Rudolf Virchow (1821 -1902) an eminent German physician {25}. He postulated a triad (called Virchow's Triad) to describe the pathogenic and pathophysiologic abnormalities within the vascular system that predisposes to thrombus formation. It consists of

- Endothelial damage
- Venous stasis
- Hypercoagulability of blood.

Most often thrombosis is the result of more than one "Hit" {26}.

Summary of pathophysiological abnormalities in HIV infection predisposing to hypercoagulability and venous thromboembolic disease. (See below for details)

- Deficiencies of antithrombotic proteins **:**
    - Protein C & Protein S
    - Heparin Cofactor II
    - Antithrombin

  Presence of procoagulants:
    - Antiphospholipid antibodies
    - Effect of endothelial cells & microparticles
    - Miscellaneous:
    - Increased Von Willibrand factor
    - Increased Tissue Plasminogen activator (tPA)
    - Increased Plasminogen activator Inhibitor (PAI-1)
    - Cytokines (TNF alpha, IL-1, IL-6)
    - Opportunistic infections & malignancies

1.3 Deficiencies of Anti-Coagulant Proteins

1.3.1 Antithrombin

Lowered levels of Antithrombin (AT) were reported in HIV infected patients with thromboembolic disease {27}. Mechanisms explaining reduced levels include inactivation by proteolytic enzymes, decreased production by the liver and increased loss via the kidneys. AT is the most crucial physiological inhibitor of activated coagulation factors (IIa, IXa, Xa, XIa and XIIa). A homogenous deficiency is incompatible with life whilst an inherited heterogenous deficiency predisposes to venous thrombosis.

1.3.2 Proteins C & S

These are vitamin K-dependent glycoproteins mainly synthesized in the liver. Both protein C and protein S levels are significantly reduced by HIV infection {28,29}. Feffer et al {28} proposed that low grade DIC in severely immunocompromised individuals with HIV and infections, inflammatory or neoplastic conditions is responsible for depressed protein C levels. He also found that D-dimer levels were elevated in HIV patients with neoplastic or inflammatory diseases. Erbe et al {29} further found that proteins C & S levels return to normal after treatment of opportunistic infections. The binding of thrombin to

thrombomodulin on endothelial surfaces activates protein C which is a potent anticoagulant. Activated Protein C (APC) inactivates the activated clotting factors V and VIII {30, 31}.

Protein S has no enzymatic action but yet an important co-factor for Protein C. 40% of Protein S is free and active whilst the majority is bound to C4 binding protein. Reduced levels of Protein S is associated with increased risk of deep venous thrombosis {32}. Diminished activity and reduced levels of protein S are also reported with HIV- infected patients {33, 34}. Postulated mechanisms for the reduced levels of protein S include increased activation or apoptosis of circulating T cells, producing microparticles that may bind protein S. Reduced levels of active protein S could also be caused by downregulation of protein S synthesis {35} or by anti-protein S antibodies {36}.

In a study conducted by Sugerman RW et al reduced concentrations of protein S were more prevalent in subjects with CD4+ T lymphocyte counts <200/mm and in HIV infected children{37}.

1.3.3 Heparin Cofactor II

HCII is a natural thrombin inhibitor and its concentration is also reportedly reduced in HIV infection. Possible explanations include decreased synthesis, enhanced proteolysis or consumption. Recurrent venous thrombosis was reported with congenital HCII Deficiency {38} even though the relationship between HCII and DVT is still debatable.

HIV-positive individuals demonstrated a greater proportion of acquired HC II deficiency than in healthy subjects {27}. Patients with AIDS have a significantly more pronounced deficiency of HC II compared with HIV patients {27}

1.4 Increase in Procoagulant Factors

1.4.1 Anti Phospholipid antibodies (APL)

The levels of antiphospholipid antibodies are increased in HIV infected patients. Various APL's are known but the most important are lupus anticoagulants and anticardiolipin antibodies. Anticardiolipin antibodies can inhibit activated protein c increasing the risk of thrombosis. APL are proteins targeting different phosphor-containing lipids, the main components of cell membranes. APL is present in 82 to 92% of patients with AIDS {39}. Increased occurrence of both venous and arterial thrombosis have been related to the presence APL {40,41}.

Lupus anticoagulants has been associated with infections by opportunistic organisms such as Pneumocystis Jiroveci. Of importance the presence of APL is not associated with the stage of the disease, CD4 cell count, viral load, medication or with a hypercoagulable state {10, 42}. An association described between microparticles and IgG-APL titers may be a consequence of microparticle generation {43}, but the mechanism remains unknown.

Polyclonal B cell expansion may also explain the elevated levels of APL in HIV infected patients {44}.

1.5 Role of endothelial cells

The normal endothelial lining act as an anticoagulant regulator. In HIV infection activation of endothelial cells play a significant role in the activation of the coagulation cascade {45-47}. Activation of endothelial cells occurred during infections with viruses including HIV {48}, Cytomegalovirus (CMV) {49}, herpes virus and many others {50-52}.

TF is the most important initiator of the coagulation cascade. It binds factor VIIa inducing the extrinsic pathway. These viral infections trigger an endothelial inflammatory response with increased expression of TF thus promoting a coagulation reaction.

Increased levels of soluble Thrombomodulim (sTM) is also noted in patients infected with HIV. It is an important co-factor for protein C so its increased concentration in HIV infected individuals denotes higher tendency for thrombosis.

1.6 Microparticles

The concentration of microparticles is much higher in patients with HIV infection {53}. Increased concentration of microparticles are associated with activation of the coagulation cascade {53}.

Microparticles are degradation products of platelets and endothelial cells found circulating in plasma. They may also originate from CD4 lymphocyte cells in HIV patients as a consequence of direct infection by the virus and apoptosis of the CD4 cells {43}. The procoagulant properties of microparticles are believed to be caused by the clustering of coagulation factor complexes on the activated phospholipid surface serving as catalysts of coagulation reactions. Even in the absence of high levels of microparticles, these elements may still contribute to enhanced coagulation activity, as seen in patients with multiple organ dysfunction syndrome and sepsis. {54}

1.7 Miscellaneous Factors

Marked elevation of Von Willebrand factor (vWF) is reported in patients with HIV {55}. Von Willebrand factor initiates the primary process in haemostasis. It is a protein derived from the endothelium that promotes adhesion of platelets to damaged epithelium. The levels of both tissue type plasminogen activator (tPA) and its inhibitor, plasminogen activator inhibitor I (PAI-I), are also found to be higher in patients with HIV {55-59}. The activation of these proteins play paramount roles in thrombosis. HIV infection can also be complicated by autoimmune haemolytic anaemia (AIHA). In this condition an increased risk of thromboembolic events, especially during infusion of red blood cells, was reported {60, 61}.

1.8 Opportunistic Infections

Despite the recent advances and effectiveness of anti-retroviral therapy HIV patients are still at increased general risk of infections. These concomitant infections remain additional established risk factors for thrombosis {1, 7, 62}. HIV/AIDS remains the greatest risk factor of TB infection with up to two thirds of HIV infected people coinfected with TB {63}. PTB is one of the most prevalent chronic infectious diseases in Africa and the tropical world {64}. Pulmonary tuberculosis is associated with a high mortality in patients with complications and an advanced stage disease. In Tuberculosis and Pneumocystis Jiroveci infection, elevated levels of APL were found in up to 94% of infected AIDS patients {65, 66}. This along with reactive thrombocytosis, elevations in plasma fibrinogen degradation products (FDP) and depressed Antithrombin III levels are mechanisms postulated to promote thrombosis in PTB patients {67}. Further studies demonstrated that these haematological parameters worsen during the first 2 weeks of anti-TB therapy in many cases but normalize after a month of anti-tuberculosis therapy {68}.

Clayton et al described a strong correlation between venous thromboembolic disease and a recent respiratory tract infection {69}.

CMV is an opportunistic infection common in HIV infections with severe immune suppression. An association between CMV infection and thrombosis has long being established. CMV infection is associated with strokes, cerebral venous thrombosis, digital infarcts, peripheral thrombophlebitis and pulmonary embolism {1, 70}.

Three main mechanisms postulated to promote the prothrombotic state in CMV infections:

- The virus can cause direct infection of endothelial cells of blood vessels increasing expression of tissue factor. This promotes an endothelial pro-thrombotic state leading to microangiopathy.
- Increased haemostatic factors such as Von Willebrand factor thus impairing fibrinolysis {1,70}
- Induction of Antiphospholipid Antibodies

Thrombotic episodes in patients with HIV and concomitant infections are much reduced with early treatment and prevention {1}.

1.9 Malignancies

Malignancies most common in HIV infected patients include Kaposi Sarcoma, Non-Hodgkin Lymphoma (NHL), anal and cervical carcinoma {1}

Other malignancies frequently observed in HIV infected patients are Hodgkin's lymphoma, multiple myeloma, leukemia, melanoma and oral, lung and anal carcinoma {76}.

Venous thromboembolic disease (VTE) is an established complication in patients with malignancy. The relationship between neoplasms and VTE has long being established {71-73}. Trousseau in 1865 was amongst the first to establish an association between occult or overt neoplasm and VTE {74}. In patients with malignancies an 8 to 10 fold increased risk of symptomatic venous thromboembolism exists. VTE still accounts for a high rate of mortality among cancer patients prior to and during the course of chemotherapy {75}.

1.10 Cytokines

Tumor Necrosis Factor (TNF), Interleukin 1 and Interleukin 6 are elevated in HIV infection {77,78}. These cytokines play an important role in the prothrombotic state of these patients and their levels are upregulated as the disease state progresses. Infection of the endothelial surface by HIV stimulate production of these cytokines which together with other acute phase reactants and opportunistic infections activate the coagulation cascade {77,79}.

1.11 JUSTIFICATION OF THE STUDY

The association between VTE and HIV infection remains controversial. Klein et al {20} did a systematic review of 10 relevant epidemiological studies relating HIV and VTE from 1991 to 2004 and found a two to tenfold increased risk in comparison with a general healthy population of the same age. However most of the studies done were retrospective cohort studies in first world with no controls. They were further limited by low absolute risk numbers with selection bias and confounding variables were not always considered. He concluded on some evidence between HIV infection and VTE but strongly advised on case-control studies to elucidate this link.

There is a high morbidity, mortality and economic burden associated with venous thromboembolic disease {3}. Kenya remains one of the six 'High Burden' countries in Africa with HIV infection. A case-control study to determine the association between VTE and HIV infection is powered enough to elucidate this link. Furthermore such a study has not been done within the sub region.

2.0 CHAPTER TWO: RESEARCH QUESTION

Is there an association between HIV infection and venous thromboembolic disease?

2.2 Null Hypothesis

There is No association between HIV infection and venous thromboembolic disease.

2.3 Broad Objectives

- To estimate the odds of VTE in HIV infected patients in comparison to age and sex matched controls without VTE.

2.4 Specific Objectives:

2.4.1 Primary Objectives:

- To determine the association between venous thromboembolism and HIV infection amongst patients at Kenyatta National Hospital.

2.4.2 Secondary Objectives:

- 1. To determine the association between venous thromboembolism and HIV infection stratified by WHO clinical stage.
- 2. To determine the association between venous thromboembolism and HIV infection controlling for traditional clinical risk factors.

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a hospital based case control study in patients with DVT and/or PE. A case of DVT was diagnosed on the basis of clinical findings and confirmed by Doppler ultrasound whilst a case of PE was diagnosed on the basis of a CTPA. Controls were subjects with no clinical evidence of DVT and/or PE matched for age and sex. A case to control ratio of 1:1 was used.

3.2 Study Area

This study was carried out at the ICU, medical, surgical, obstetrics & gynaecology wards and the VCT center of Kenyatta National Hospital.

3.3 Case definition and selection

The study population consisted of patients with deep venous thrombosis and/or pulmonary embolism and equal number of age and sex matched control.

Case: Patients with clinical and Doppler evidence of proximal or distal DVT and/or patients with PE confirmed by CTPA admitted to the wards or ICU of Kenyatta National Hospital.

3.3 Controls and selection of control group

Control: Consecutive sampling among individuals without clinical evidence of DVT and/or PE who presented to the VCT center for voluntary HIV testing during study period. They were matched for age and sex. Matching for the age was within a range of five years (age of case+_ 5 years).

3.4 Inclusion criteria of case:

- Patients > 18 years of age
- Patients with clinical and Doppler evidence of DVT and/or patients with PE confirmed by CTPA.
- Written informed consent
- Patients admitted to the wards or ICU during the period of study.

3.4.1 Inclusion criteria of control:

- Sex and age matched individuals of unknown HIV status and without any clinical evidence of DVT and/or PE who visit the VCT center for voluntary HIV testing.
- Age > 18 years
- Written informed consent

3.5 Exclusion criteria of case and control:

There was no exclusion criteria once the inclusion criteria was met

3.11Sample Size Determination

A retrospective review of files of patients with DVT for one year (e.g. APRIL 2016 TO APRIL 2017) at the Kenyatta National Hospital puts the incidence of HIV at 28.0%. The prevalence therefore will approximately be 28% (prevalence = incidence x duration). The prevalence of HIV at the Nairobi County according to the National AIDS Control Council (NACC, 2014) is 6.8%.

The study used the prevalence of HIV in VTE patients and the County prevalence to calculate the sample size using Kelsey formula (Kelsey et al. 1996)

Ref: Kelsey J.L, Whitmore A.S, Evans A.S and Thompson W.D. Methods in Observational Epidemiology 2nd Edition, Oxford University Press, 1996 Print

$$\boldsymbol{n_1 = \frac{\left(Z_{\propto/2} + Z_{1-\beta}\right)^2 p(1-p)(r+1)}{r(p_0 - p_1)^2}}$$

And

$$\boldsymbol{n_2 = rn_1}$$

Where,

n_1= number of cases

n_2= number of controls

$Z_{\propto/2}$= standard normal deviate for two-tailed test corresponding to 95% CI i.e. 0.05

$Z_{1-\beta}$= standard normal deviate corresponding to power level of 80% i.e. 0.842

r = ratio of controls to cases i.e. 1

p_0 = proportion of DVT patients with HIV i.e. 0.28

p_1= proportion of people living with HIV in Nairobi County i.e. 0.068

$$\boldsymbol{p = \frac{p_0 + rp_1}{r + 1}}$$

$$\boldsymbol{p = \frac{0.28 + (1\,x\,0.068)}{1 + 1} = 0.174}$$

$$\boldsymbol{n_1 = \frac{(1.96 + 0.842)^2 0.174(1 - 0.174)(1 + 1)}{1(0.28 - 0.068)^2} = 51}$$

Therefore,

$$\boldsymbol{n_2 = 1\,x\,51 = 51}$$

The study therefore required a minimum of 51 cases and 51 controls

3.6 Clinical Method

This was a hospital based case control study of patients with confirmed VTE (DVT and/or PE) diagnosis admitted to the ICU, medical, surgical, obstetrics and gynaecology wards of KNH. Consecutive sampling of all cases of VTE admitted to KNH during my study period was done until the target sample size was met. As the Principal Investigator (PI) in this research, the help of a research assistant (clinical officer) was sought to help in identifying cases and controls and in data collection. The research assistant was working with the PI to ensure that data was collected efficiently, on time and that it was recorded accurately. All recorded data was verified by the PI, who also ensured that all relevant forms were completed. The health care workers in the study area were notified about the intended study by way of a circular informing the principal investigator or the research assistant about patients with VTE. Furthermore in a proactive manner, either the PI or research assistant on alternate day basis were visiting the desired wards to look for cases to be included into the study.

Upon identification of a case, the participant was counselled about the study and a written and well explained consent form in English (or translated version in Kiswahili) was provided for signing. Adequate privacy was maintained throughout the process. A data collection Form (copy attached) was provided for completion by the patient (if literate) or assisted by the PI or research assistant. The participant was interviewed and relevant variables such as age, gender, smoking history, history of pregnancy OCP & HRT use (for females), recent history of surgery within the past 4 weeks, immobilization, travelling or lower limb casting was noted down. A personal or family history of previous DVT or PE was sought. The weight and height were assessed and BMI computed by the PI or research assistant. The participant was only examined by the PI and along with the clinical notes evidence of Heart failure and Tb was also documented (if any). If the HIV status of the case was already documented in the file then the details are jotted into our data collecting form. For HIV positive patients, the CD4 count, viral load, WHO clinical staging and HAART regimen (if any) were documented. For those without known status, the patient underwent pre-test counselling by the counselor before the test was done and the result was disclosed and documented. A post-test counselling was also offered. Those incidentally found to be positive were counselled and advised on partner check (if any) and the need to do further tests and commence anti-retroviral drugs. No identity of any patient was disclosed during this research. No case was coerced to participate in this study.

A written and well explained consent form was issued to all age and sex matched control individuals participating in this study. The controls were selected among individuals who voluntarily seek HIV testing at the VCT center of Kenyatta National Hospital. Consecutive sampling of controls matched for age (+/_ 5 years) and sex was done until the target study population size was met. The purpose of the study was clearly explained and a consent form was provided for signing. Adequate privacy was maintained throughout the process. A brief medical history to exclude present or past DVT and/or PE was undertaken before inclusion into the study. Following the consent, the data collecting tool was provided to the participant or supported by the PI or research assistant for filling. All relevant variables as per a case are determined and documented. The BMI was then obtained by the PI or research assistant. The controls were only examined by the PI and all variables as per a case were documented. The result of the test was disclosed to the control subject by the counsellor. A post-test counselling was also done. Incidental positive cases were advised on partner check (if any) and the need to do further tests and start anti-retroviral drugs. Those found to be negative were also disclosed and counselled on good behavior.

3.7 Definition of outcome variables

- **Age**
- **Sex**
- **BMI:** Underweight < 18.5 kg/m2, Normal weight 18.5 – 25 kg/m2, Overweight 25 – 30 kg/m2, obese > 30 kg/m2.
- **HIV status:** Positive or Negative confirmed by Rapid HIV test strip
- **WHO HIV Clinical Stage:** stage 1, stage 2, stage 3, stage 4.
- **Pregnancy:** Current, Puerperium, abortion
- **Bed ridden or immobilized:** > 3 days
- **Surgery:** major or minor within the past 4 weeks
- **Long distance seated travelling** (>6 hours) within past 2 weeks
- **Use of OCP:** Current (within the past 3 months), Past (used for >1 year but stopped > 3 months ago).

- **Use of HRT:** Current (within the past 3 months), Past (used for >1 year but stopped > 3 months ago).
- Previous personal **history of DVT and/or PE.**
- **Family (1st degree relative) history** of DVT and/or PE.
- **Orthopedic casting** within the past 1 month.
- **Heart Failure:** Based on Framingham criteria
- Diagnosis of Pulmonary **Tuberculosis:** CXR, Sputum AFB positive or Genexpert
- **Smoking**
- Current smoker: smoked > 100 cigarettes in their lifetime, has smoked the last 28 days
- EX-smoker: has smoked > 100 cigarettes, has not smoked the last 28 days.
- Never smoker: has not smoked > 100 cigarettes in their lifetime, does not currently smoke.
- Social/occasional smoker: smoke usually only when socializing, at least once a week.

3.8 Feasibility and Logistics

In a pilot survey of the wards of Kenyatta National Hospital where cases were obtained from, it was estimated that at least one case of VTE was admitted per ward per week. Considering the minimum number of cases needed (51) for this study, it was estimated that the desired number of cases would be obtained within 8 – 10 weeks.

As recommended by the 2016 HIV National Guidelines, routine opt – out provider initiated HIV testing and counselling (PITC) is offered to all clients/patients seeking care at KNH regardless of the admission diagnosis. As a result the HIV status (which is the primary variable of our study) of all cases to be included were very likely to be known and documented already in the files. HIV test is done free of charge. In cases whose HIV status was unknown, thorough counselling and consent was taken before we proceeded. Any information obtained was kept strictly confidential.

A review of HIV testing at the VCT center of KNH reveal an average of 40 - 45 individuals seek voluntary testing per day. The age ranges from 18 – 65 years. As a consequence recruiting controls for this study was easily met.

Throughout the process my supervisors offered guidance on my project development whilst my statistician was supporting in data management and analysis.

3.9 Ethical Approval

This study was approved by the Department of Clinical Medicine and Therapeutics, University of Nairobi and Kenyatta National Hospital Ethics and Research Committee. Permission was sought from all heads of departments of respective study sites before any procedure or data collection was carried out. Only patients who gave written consent were recruited into the study. A translator was sought for patients who did not understand English or Kiswahili. No patient was coerced to participate in the study. All participants recruited were given identifier number and the information obtained was kept strictly confidential by the PI in a password protected computer. No identity of any patient was disclosed along the whole process. It was also made clear to all participants that there was no reimbursement or gift awarded to participate in the study. Participants incidentally diagnosed to be HIV positive were counselled by the HIV counselor and advised on partner check (if any) and the need to commence HAART.

3.10 Data Management and Analysis:

The data was collected, entered and analyzed using SPSS version 21 statistical package. The demographic, history and examination data was analyzed and presented as frequencies and proportion; where applicable mean with standard deviations and median was calculated. The results were presented in the form of tables and charts. The association between HIV seropositive status and development of venous thromboembolic disease was done using univariate analysis and odds ratio. Multivariate logistic regression analysis was done to determine the association between HIV seropositive patients and development of venous thromboembolism controlling for other traditional clinical risk factors. The professional service of a qualified statistician was sought to help during proposal development, data entry and analysis.

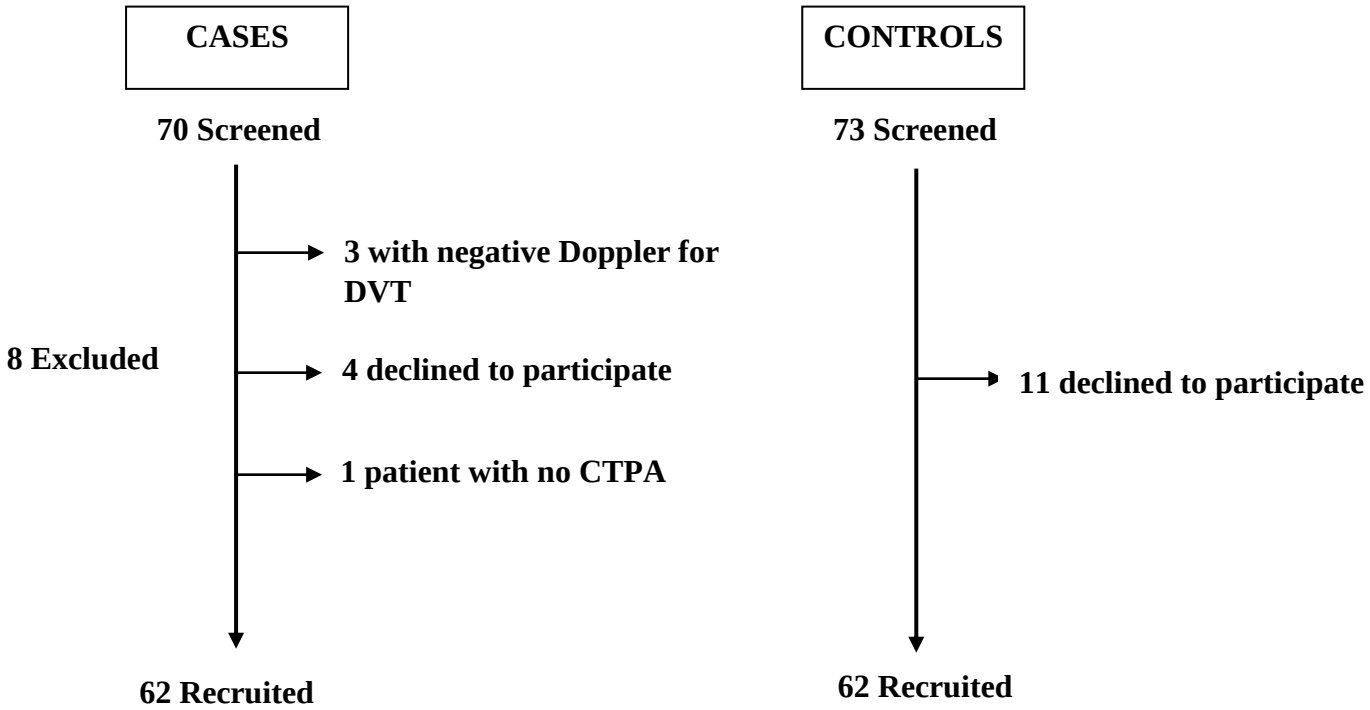
4.0 CHAPTER FOUR: RESULT PRESENTATION AND ANALYSIS

4.1 Introduction

This study was undertaken at Kenyatta National Hospital (KNH) from January 2018 to April 2018. The primary objective of the study was to establish if there is an association between Venous Thromboembolism (VTE) and HIV infection. A total of 124 participants were enrolled into the study comprising 62 cases of VTE obtained from the ICU, medical, surgical, obstetrics and gynecology wards, and 62 controls without clinical signs and symptoms of VTE from the Voluntary Counselling Test (VCT) Centre of Kenyatta National Hospital.

A consecutive sampling method of VTE cases admitted to the wards was done until our target sample size was met. 70 cases were recruited to participate in the study. 8 cases were excluded (3 had a negative Doppler ultrasound scan of the lower limbs for DVT, 4 declined to participate in the study whilst 1 patient with suspected PE was unable to have a CTPA done) thus 62 recorded. At the VCT center 73 participants were screened, 11 declined to participate in the study thus 62 recorded.

Flowchart of participant recruitment



Of the 62 cases of VTE, 52 (83.9%) had a deep vein thrombosis (DVT) whilst the remaining 10 (16.1%) had pulmonary thromboembolism (PTE). Left lower limb DVT was the most common 39 (62.9%) compared to the right 11 (17.7%).

4.2 Demographic Information

Table 1: Distribution of baseline characteristics of cases and controls

	Frequency n (%)	
	Cases	**Controls**
Age in Years	**N = 62**	**N = 62**
13-22	3 (4.8)	4 (6.5)
23-32	23 (37.1)	26 (41.9)
33-42	23 (37.1)	19 (30.6)
43-52	4 (6.5)	4 (6.5)
53-62	9 (14.5)	9 (14.5)
Gender		
Male	21 (33.9)	21 (33.9)
Female	41 (66.1)	41 (66.1)
HIV Status		
Positive	23 (37.1)	7 (11.3)
Negative	39 (62.9)	55 (88.7)

Since the cases and controls were matched for age and sex there was no significant difference in their characteristics. 21 (33.9%) of the cases were males and 41 (66.1%) were females. Most of the cases were between the ages of 23-32 years (49 [39.5%]), followed by 33-42 years (42 [33.9%]) with a mean (SD) age of 36.2 (10.9) years and a median age of 35 years with an interquartile range of 13 years.

HAART regimen and documented CD4 and Viral Load

30 study subjects were HIV infected, 23 cases and 7 controls. Of the 23 cases with HIV, 1 (4.3%) was newly diagnosed and HAART naïve, 21 (91.3%) were on first line treatment and 1 (4.3%) was on second line ARV's. All the HIV positive controls were newly diagnosed and were HAART naïve.

Only 10 of the HIV positive cases had a recently (within the past 6 months) documented CD4 count with 50% having a count between 0 – 250 cells and the other 50% between 251 – 500 cells. Only 4 of the HIV positive cases had their viral load documented.

Table 2 : Distribution of risk factors between cases and controls

	Frequency n (%)		OR	p-value	95% CI for OR
	Cases	Controls			
Pregnant within the past 1 month	9 (14.5)	3 (5.8)	3.56	0.068	0.89 – 14.28
Current or past use of Oral Contraceptive Pills	29 (46.8)	32 (51.6)	0.68	0.590	0.25 – 1.85
History of Cancer	17 (27.4)	1 (1.6)	23.04	<0.001	2.98 – 179.59
Had any type of surgery (major or minor) within the past 4 weeks	14 (22.6)	2 (3.2)	8.75	0.001	1.89 – 40.39
Major trauma within the past 1 month	4 (6.5)	1 (1.6)	4.21	0.171	0.46 – 38.78
Long distance travelling within the past 2 weeks	16 (25.8)	14 (22.6)	1.19	0.675	0.52 – 2.72
Recent Central Venous Catherization	9 (14.5)	0 (0.0)	-	0.002	-
Pulmonary Tuberculosis	13 (21.0)	0 (0.0)	-	<0.001	-
Smoking	16 (25.8)	15 (24.2)	1.09	0.836	0.48 – 2.46

In this univariate analysis history of cancer (p=<0.001), recent surgery within the past 4 weeks (p=0.001), recent central venous catheterization (p=0.002) and pulmonary tuberculosis (<0.001) achieved statistical significance.

4.3 Analysis of Primary and Secondary Objectives

Table 3: Association between VTE and HIV seropositive status

		Cases (VTE)	Controls (No VTE)	Total	Odds Ratio	P- value	95% CI for Odds Ratio
HIV	+	23	7	**30**	4.634	0.001	1.810 – 11.866
	-	39	55	**94**			
		62	**62**	**124**			

To determine the association venous thromboembolism and HIV infection a univariate analysis with calculation of odds ratio was done. The analysis reveals that the odds of having VTE in an HIV positive patient was 4.634 times (p=0.001, CI 1.810 – 11.866) than of HIV negative patients.

Table 4: Distribution of cases and controls stratified by WHO clinical staging

WHO Clinical Stage	Cases (%)	Controls (%)
I	1 (4.3)	7 (100)
II	8 (34.8)	
III	12 (52.2)	
IV	2 (8.7)	

The first secondary objective was to determine the association between venous thromboembolism and HIV infection stratified by WHO clinical staging. Seven of the 62 controls were HIV positive and were all in stage I. on the other hand, of the 62 cases 23 were HIV positive and were distributed amongst the 4 WHO clinical stages of HIV infection as shown above. As a result of this distribution, this objective could not be met.

The other secondary objective was to determine the association between venous thromboembolism and HIV infection controlling for traditional clinical risk factors. This was adjusted for all the factors in table 2 namely pregnancy, use of oral contraceptives, smoking, recent trauma, cancer, long distance travelling, being recently bed-ridden and surgery. Recent central venous catheterization and pulmonary tuberculosis were not included into the logistic regression model as there were zero controls and thus the odds ratio cannot be calculated. This was done so to establish if some of the risk factors found not to be statistically significant in the univariate analysis remained so when adjusted for in a multiple regression model. HIV positive status remained an independent risk factor of VTE with the patients having about 7-fold increased chance of the disease compared to the HIV negative patients [aOR 6.6 (95% CI 1.7-25.6), p=0.006].

Similarly, there was a higher risk of VTE among patients who reported pregnancy [aOR 6.1 (95% CI 1.2-32.4), p=0.033], cancer [aOR 28.1 (95% CI 2.9-271.1), p=0.004], recently bed-ridden [aOR 22.2 (95% CI 2.6-190.4), p=0.005] and those who have had a recent surgery [aOR 6.8 (95% CI 1.2-39.7), p=0.033].

5.0 CHAPTER FIVE: DISCUSSION

In addressing the primary objective of this study to ascertain an association between VTE and HIV infection, a univariate analysis with calculation of odds ratio was done. The analysis reveals that the odds of having VTE in HIV positive patients is 4.634 times than of HIV negative patients. These findings are in comparison with previous studies and the systematic review of 10 major epidemiologic studies in the United States by Klein et al {20} which revealed that HIV infected patients had a 2 to 10 fold increased risk of developing a VTE compared to the general population. Despite the environmental and ethnic differences between participants of my study and that of the systematic review the findings are comparable. However most of the previous studies reviewed by Klein et al were retrospective cohort study in the United States with selection bias. There were no controls and confounding factors were not always included. Being a case control study on the other hand, my study is empowered by having a control arm and thus controlling for traditional risk factors. Throughout my research I could not find any published case control study looking at the association between VTE and HIV infection within the sub region thus making my study to be the first.

The first part of the secondary objective which was to determine the association between venous thromboembolism and HIV infection stratified by WHO clinical stage of HIV infection could not be achieved as all the controls that were HIV positive were in stage I compared to the HIV positive cases which were distributed amongst all the 4 WHO clinical stages of HIV infection. This could however be logically explained as our controls were relatively ‘Healthy individuals’ who voluntarily walk into a VCT center to get their status checked and thus were in the early stages of their disease.

The most commonly documented traditional risk factors in the cases of VTE were current or past use of OCP 29 (46.8%), cancer 17 (27.4%), smoking 16 (25.8%), long distance travelling 16 (25.8%), recent surgery (within the past 4 weeks) 14 (22.6%) and pulmonary tuberculosis 13 (21.0%).

HIV/AIDS remains the greatest risk factor of TB infection with up to half of TB patients coinfected with HIV {63}. PTB is one of the most prevalent chronic infectious diseases in Africa and the tropical world {64}. Increased levels of APL were found in up to 94% of infected AIDS patients with PTB {65, 66}. This along with reactive thrombocytosis, elevations in plasma fibrinogen degradation products (FDP) and depressed Antithrombin III levels are mechanisms postulated to promote thrombosis in PTB patients.

Of the 62 cases recruited into the study 23 were HIV positive. In a retrospective review by Ogeng'o et al {80} in 2011 to describe the pattern of PTE among black Africans at Kenyatta National Hospital he reviewed the records of patients with PTE seen between January 2005 and December 2009 to ascertain mode of diagnosis, comorbidities, age, gender, treatment and outcome. The prevalence of HIV in the 128 cases reviewed is 10.9% which is much lower than findings of my study (37.1%). This finding could be explained by the recommendation of the 2016 HIV National Guidelines of routine opt – out provider initiated HIV testing and counselling (PITC) offered to all patients seeking care at KNH regardless of the admission diagnosis. As a result more HIV cases are detected lately.

Seventeen of the cases had an underlying malignancy or undergoing treatment for one. Carcinoma of the cervix was the most common 4 (23.5%). In a retrospective study by Saif et al {1} of 131 HIV- infected patients he found DVT to be more common in HIV positive patients with advanced disease and AIDS defining malignancies (carcinoma of the cervix, kaposis sarcoma and non-Hodgkin's lymphoma). The relationship between neoplasms and VTE has long being established {71 – 73}. Trousseau in 1865 was amongst the first to establish an association between occult or overt neoplasm and VTE {74}.

Of the 23 HIV positive cases only 10 had a recently (within the past 6 months) documented CD4 cell in their files. The 2016 national HIV guidelines however recommend a baseline CD4 count with repeat only if treatment failure was suspected. This along with a recent shortage of CD4 count reagents could explain the absent documentation of their recent CD4 count. 50% of these cases (5) had a CD4 count of <250 cells. This with a slight variation supports previous studies done by Saif et al {1} which further concluded that abnormalities of hyper coagulation correlate with the degree of immune suppression and found VTE to be more common in HIV patients with CD4 count of <200 cells. In a retrospective study in 1996

by Laing et al {15} looking at venous thrombosis in HIV patients, he found the incidence of VTE to be up to 2 times higher in patients with full blown AIDS.

The second secondary objective was to determine the association between HIV seropositive status and occurrence of venous thromboembolism controlling for other traditional clinical risk factors; history of cancer, smoking status, pregnancy within the past one month, use of oral contraceptive pills, surgery within the past 4 weeks, and bed-ridden/paralysis. A multiple logistic regression model was done and these risk factors were included in. Recent central venous catheterization and pulmonary tuberculosis were not adjusted for as there were no controls with these diseases and thus an odds ratio could not be calculated. After controlling for the above risk factors, HIV remained an independent risk for VTE with an adjusted odds ratio 6.6. This sustained risk of about 7 folds further supports previous studies by Klein et al {20} which revealed HIV positive patients have a 2 to 10 fold increased risk of developing VTE compared to HIV negative people.

5.1 Conclusions

HIV is a risk factor for venous thromboembolism. The odds of VTE in an HIV infected person is 5 to 7 times higher than that of an HIV negative person.

After controlling for other risk factors, HIV remained an independent risk for VTE.

5.2 Strengths of the study

- A case control study controlling for risk factors
- Primary specific objective was met
- First case control study of VTE in association to HIV in the sub region

5.3 Limitations

i. This study was conducted in a single national referral hospital and may not be generalized to the entire country
ii. This study was only able to establish an association and not a cause-and-effect relationship between HIV infection and venous thrombosis
iii. Incomplete data (CD4 count / viral loads) for most HIV patients.

5.4 Recommendations

i. All patients suspected to have VTE should be screened for HIV given the 7 fold increased risk for VTE in HIV positive compared to the general population.

ii. Similar studies should be carried out on a larger scale nationwide involving many health care centers with a larger population size.

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APPENDICES

Appendix I: Data Collecting Form

Study No:

Name (initials):

Age:

Sex: Male Female

Occupation:

Residence:

HIV Status: Positive Negative

For Females:

LNMP:

Are you pregnant or recently been pregnant within the past 1 month? Yes No

Any current or past use of Oral Contraceptive Pills? Yes No

Any current or past use of Hormone Replacement Therapy? Yes No

Any history of cigarette smoking? Yes No

If Yes, when and for how long?

Smoking result: Never smoker

Current smoker

Former smoker

Social smoker

Any previous history of Venous Thromboembolism (DVT or PE) apart from this one?

If yes, when?

Any first degree family history of VTE (DVT or PE)? Yes No

Any recent history of paresis or paralysis within the past 1 month? Yes No

Any documented evidence of cancer of any sort or have received medications for cancer within the past 6 months? Yes No

If yes, where is the cancer?

Have you recently been bed ridden for > 3 days? Yes No

Have you had any type of surgery (major or minor) within the past 4 weeks? Yes No

If yes, what type of surgery?

Have you had any recent orthopedic casting of the lower extremities?

Yes No

Have you had any major trauma within the past 1 month?

Yes No

Any history of long distance seated travelling within the past 2 weeks:

Yes No

Any history of recent Central Venous Catheterization done?

Yes No

Examination:

Weight: Height: Calculated BMI:

BMI Result: underweight normal weight overweight obese

Any evidence of Heart Failure? : Yes No

Any evidence of Arrhythmias? : Yes No

Any evidence of Pulmonary Tuberculosis? : Yes No

Any evidence of Nephrotic Syndrome? : Yes No

FOR HIV POSITIVE PATIENTS

WHO Clinical Staging: stage 1 stage II stage III stage IV

Documented last CD4 count (within past 1 year):

Documented Viral load

HAART regimen:

- Newly diagnosed, HAART naïve
- First line ARV's
- Second line ARV's
- Third line ARV's

Any documented history of opportunistic infection:

- Cryptococcal meningitis
- Toxoplasmosis
- Tuberculosis
- Any other

Appendix II (a): Consent Explanation (English)

Study Title: HIV as a risk factor for venous thrombosis; A case-Control study at Kenyatta National Hospital

Introduction:

My name is Dr. Ibrahim Huballah, a postgraduate student of the University of Nairobi based in Kenyatta National Hospital. As a partial fulfillment for my master's degree in Internal medicine, I am expected to perform a research study. My research study is on whether there is a relationship between venous thrombosis (which is a blood clot that usually occurs in the legs or lesser extent arms causing pain and swelling and can spread to the lungs) and HIV infection.

Why have you been invited to join this study?

Your lab and imaging results are showing you have a blood clot in your legs/lungs. You are therefore eligible to participate and I would therefore, like to invite you to join this study.

Reason for the study:

We are doing this study because it will help us understand better the risk factors for clots in the legs/arms/lungs and guide doctors on its management. This is a life threatening condition and a better understanding of its causes and treatment would help us in saving lives of people.

What do I need to do?

The first step is reading through this consent from and agreeing to join the study. My research assistant or I will then give you a questionnaire to answer. These questions are trying to identify any reason/risk factor for you getting the blood clot. Please feel free to ask any question or seek any clarification as we proceed.

After filling the questionnaire, I will perform a general physical examination. This will take about 20 minutes and will be done on your hospital bed with the curtains drawn. If you have been tested for HIV and your results are in your medical records, we will use those results for this study. If you haven't been tested for HIV, a counselor will take you through HIV pretest counseling and as soon as you are ready, perform a rapid HIV test. Your finger will be pricked to obtain a small amount of blood for testing. The results of your test will be disclosed to you in ten minutes and will be followed by a post-test counseling session. If your

HIV results aren't in the records and you do not wish to be tested, you will be excluded from the study.

Are there any risks of participating in this study?

There may be mild discomfort during the physical examination, but I will endeavor to be as gentle as possible.

The finger pin prick for HIV testing may cause very minimal discomfort. This is very short lived.

Are there any benefits of participating in this study?

Your treatment will be improved and will be for a clearer duration of time, as treatment of blood clots is guided by the cause.

You will leave the hospital aware of your HIV status and receive appropriate counseling and management on the same.

Please note that no cash or gifts will be awarded to you for participation in this study.

Confidentiality:

Your identifiers (name, hospital number) will not be disclosed to anybody during this study.

The data or results collected here will be kept strictly confidential .Any information you share impacting on your current treatment for the blood clot will be shared only with the doctors taking care of you to improve your care.

Thank you for reading this far. You are now welcome to sign the consent form below if you are ready to join the study. There will be no negative impact on your current management if you choose not to join the study. After consenting, you may discontinue from the study at your discretion at any time if you wish to.

Consent Form

I …….. do hereby voluntarily agree to take part in this research study of HIV association in patients with venous thrombosis at Kenyatta National Hospital. The procedure and benefits of this study has been clearly explained to me by Dr. Huballah/his assistant and I have been assured that there is no risk of my participation. I have not been financially encouraged in any way to participate in this study. The results of my test would be disclosed to me and whatever information gathered would be kept strictly confidential. In respect thereof I agree to take part in this study.

Signed ……

Witnessed ……

Date …….

In case of any questions concerning the study, contact Dr. Huballah through 0791009567.
Email: huballahdr@gmail.com

In case of any ethical concerns, please contact:
The Chairman,
KNH/UON Ethics and Research Committee,
P.O. Box 20723, Nairobi (00202)
Hospital Road, off Ngong road.
Telephone number-254-020-2726300 ext. 44355
Chairperson: Professor A.N. Guantai
Contact person: Esther Wanjiru Mbuba
Email: uonknh_erc@uonb.ac.ke

Details of my lead supervisor is as follows:
Name: Dr. Jared. O. Mecha
Consultant physician/pulmonologist
Lecturer, Department of Clinical Medicine & Therapeutics
University of Nairobi
Tel: 0722-842-741
Email: jomecha@gmail.com

Appendix II (b): Consent Explanation (Swahili)

Fomu ya maelezo;

Mada ya utafiti: Uhusiano kati ya virusi vya ukimwi na ugonjwa wa kuganda damu mishipani katika kikundi cha wagonjwa wanaotibiwa ugonjwa wa kuganda damu katika hospitali kuu ya Kenyatta.

Kielelezo;

Jina langu ni Daktari Ibrahim Huballah-mwanafunzi wa Chuo Kikuu cha Nairobi,Idara ya matibabu ya watu wazima kwa kutumia dawa.Ili nituzwe shahada ya juu(uzamili)-ninahitajika kufanya utafiti. Utafiti wangu unangalia uhusiano kati ya ugonjwa wa kuganda damu mishipani(mara mingi miguuni,mikononi au kwenye mapafu) na uwepo wa virusi vya Ukimwi.

Je,nimealikwa kujiunga na utafiti huu kwa nini?

Vipimo vyako vya picha na damu vimeonyesha kwamba umeugua ugonjwa huu wa damu kuganda mishipani. Wagonjwa wote wanaotibiwa ugonjwa huu watanufaika kujiunga na utafiti huu na ninaomba ujiunge na utafiti huu.

Je,ninahitajika kufanya nini?

Jambo la kwanza ni kusoma maelezo haya halafu uweke sahihi fomu ya makubaliano kujiunga na utafiti huu.Baada ya hapo,mimi au msaidizi wangu tutakupa fomu yenye maswali uyajibu.Maswali haya yanajaribu kutambua sababu /chanzo chako cha kuugua ugonjwa huu wa kuganda damu mishipani. Wakati wowote ukiwa na swali au kitu hujaelewa-kuwa huru kuuliza maelezo zaidi. Baada ya kujibu maswali hayo,nitakupima mwili wako kutambua dalili zozote za mgando wa damu mishipani.Kipimo changu kitachukua muda wa dakika ishirini na nitakupima kitandani pako kama tumefunga pazia.

Baada ya hapo-tutapitia rekodi zako za matibabu hospitalini kuangalia kama umepimwa virusi vya ukimwi.Kama tayari umepimwa,tutatumia ripoti hiyo kwa utafiti huu. Kama hujapimwa,mshauri atakuja,akuelezee kwa ufupi manufaa na jinsi atakavyopima ,na ukikubali,akupime.Atakupima kwa kutoa damu kidogo kidoleni.Matokeo ya kipimo chako yatakuwa tayari baada ya dakika kumi na utapewa mawaidha ya jinsi utakavyoishi kulingana na matokeo yako. Kama hujapimwa virusi vya ukimwi na hutaki kupimwa,hutaweza kujiunga na utafiti huu.

Je,kuna athari zozote za kujiunga na utafiti huu?

Nitakapokupima kitandani,kuna uwezekano utahisi maumivu kidogo.lakini nitajaribu kabisa nisikuumize .

Kipimo cha virusi vya ukimwi kinasababisha maumivu kidogo kidoleni,lakini ni ya muda tu.

Je,nitanufaika kivipi nikijiunga na utafiti huu?

Matibabu yako yataboreshwa na muda unaohitaji matibabu kwa ugonjwa wa kuganda damu mishipani itatambulika kikamilifu ,kwani chanzo cha damu kuganda mishipani ndio huangaliwa ili daktari akupangie muda wa matibabu. Utaondoka hospitalini kama umejua hali yako ya HIV na kama umepata ushauri wa kuishi maisha mema kama umetambulika kuwa na virusi vya ukimwi. Hatutakupa pesa au zawadi zozote kukushindikiza kuingia utafiti huu.

Usiri:

Jina lako na nambari ya hospitali hayatatumika kama vitambulizi vyako katika utafiti huu. Matokeo ya utafiti na ripoti za vipimo vyako vitawekwa siri kabisa.Mambo yoyote ya kibinafsi ambayo utatueleza yanayogusia matibabu yako ya ugonjwa wa kuganda damu yatawasilishwa kwa daktari /madaktari wanaokutibu pekee yao,ili kuboresha matibabu yako.

Asante kwa kusoma maelezo haya. Nakukaribisha ujiunge na utafiti huu kwa kuweka sahihi fomu ya makubaliano ifuatayo. Kama hutajiunga na utafiti huu,hutaathirika kwa matibabu yako kwa njia yoyote. Pia,baada ya kujiunga ukiamua kujiondoa unaweza kujiondoa bila madhara yoyote.

Fomu Ya Makubaliano:

Mimi ……, nimekubali kwa hiari yangu kujiunga na utafiti huu wa uhusiano kati ya virusi vya ukimwi na ugonjwa wa kuganda damu mishipani,unaofanywa katika Hospitali kuu ya Kenyatta.

Nimeelezwa utaratibu na maelezo yote kuhusu utafiti huu na Daktari Huballah/msaidizi wake na nimeahidiwa hakuna hatari za kujiunga na utafiti huu.

Sijapewa pesa au shinikizo lolote kujiunga na utafiti huu. Matokeo ya vipimo vyote nitafanyiwa nitaelezwa na maelezo yangu binafsi yatawekwa siri. Hivyo basi nimekubali kujiunga na utafiti huu.

Sahihi ……

Shahidi ……

Tarehe ……

Appendix III: Study Registration Certificate

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   IBRAHIM - S - HUBALLAH
2. Email address: huballahdr@gmail.com Tel No. 0791009567
3. Contact person (if different from PI) N/A
4. Email address: N/A Tel No. N/A
5. Study Title
   HIV INFECTION AS A RISK FACTOR FOR VENOUS THROMBOSIS: A CASE - CONTROL STUDY AT KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted MEDICINE
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ..... Signature ..... Date .....
8. Endorsed by Head of Department where study will be conducted.
   Name: ..... Signature ..... Date 23/1/18
9. KNH UoN Ethics Research Committee approved study number P636/11/2017
   (Please attach copy of ERC approval)
10. I DR. IBRAHIM - S - HUBALLAH commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature ..... Date 22/01/18
11. Study Registration number (Dept/Number/Year) Medic/NATIONAL/127/2018
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL 24 JAN 2018 P.O. Box 20723-00202 NAIROBI

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014

Appendix IV: Approval to Conduct Study, Medicine Department, KNH

KENYATTA NATIONAL HOSPITAL
P. O. Box 20723, 00202 Nairobi

Tel: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/AD-MED/42B/VOL.I/

Date: 22nd January 2018

Dr. Ibrahim S. Huballah
Department of Clinical Medicine & Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

RE:APPROVAL TO CONDUCT A STUDY IN MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration certificate, permission is hereby granted for you to collect data from Medicine Department to enable you complete your study on ***"HIV infection as a risk factor for venous thrombosis; A case control study at*** Kenyatta *National Hospital, Nairobi County, Kenya.*

Kindly liaise with the Senior Nursing Officer Incharge Medicine Department for facilitation.

DR. P.ETAU
HOD - MEDICINE

Copy to: Senior Nursing Officer Incharge - Medicine Department

Vision: A world class patient-centered specialized care hospital

ISO 9001: 2008 CERTIFIED

Appendix V: KNH/UoN- ERC Letter of Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
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Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
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Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 15 JAN 2018 KNH/UoN-ERC P.O. Box 20723-00202 Nbi

Ref: KNH-ERC/A/25

15th January 2018

Dr. Ibrahim S. Huballah
Reg. No.H58/82828/2015
Dept. of Clinical Medicine and Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Huballah

RESEARCH PROPOSAL: "HIV INFECTION AS A RISK FACTOR FOR VENOUS THROMBOSIS. A CASE-CONTROL STUDY AT KENYATTA NATIONAL HOSPITAL (P636/11/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 15th January 2018 – 14th January 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) 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*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Protect to discover