PREVALENCE OF ACUTE DEEP VEIN THROMBOSIS IN HIV SEROPOSITIVE ORTHOPAEDIC PATIENTS AFTER MAJOR SURGERY AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

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A dissertation submitted to the University Of Zambia in partial fulfillment of the require ements for the Master of Medicine in Orthopaedic and Trauma Surgery

THE UNIVERSITY OF ZAMBIA

LUSAKA

2019

DECLARATION

I hereby declare that this dissertation herein presented for the degree of Master of Medicine (Orthopaedic and Trauma Surgery) has not been previously submitted wholly or in part for any other degree at this or any other university nor is it being currently submitted for any other degree,

Signed……(Candidate)

by……..(Supervisor 1)

Approved

by……..(Supervisor2)

APPROVAL

This dissertation of DR COLLIN WEST is approved as fulfilling part of the requirements for the award of degree of Master of Medicine in Orthopaedic and Trauma Surgery by the University of Zambia, subject to the examiner's report

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Chairperson Board of Examiners.....

Signatures..... Date.....

Supervisor.....

Signature..... Date.....

ABSTRACT

Hypercoagulable states and immobilization are known risk factors in the development of DVT after major orthopaedic surgery. However, the added effect of HIV to major orthopaedic surgery in developing DVT is unknown. In addition the benefits of D-dimer screening of patients after major surgery is not emphasized. A total of 42 Patients, 23 (54 %) were HIV negative (control) and 19 (46 %) were HIV positive were recruited by convenient sampling. Prior to surgery demographic and HIV status data was recorded. After surgery a blood sample was tested for D-dimer levels. The patients were then monitored acute DVT clinically and confirmed by ultrasound. The HIV positive cohort recorded 19 (46%) and the control (HIV negative) cohort recorded 23 (54%) participants. The results showed no significant difference in the development of acute DVT; (5.3%) in the HIV positive group and (4.3%) in the HIV negative group. In addition, no significant difference between the two groups in the number of positive D-Dimers, (97.7%) in the HIV positive cohort and (95.7%) in the HIV negative cohort group. In both cohorts, hip and knee surgeries had high values for D-Dimers. There was a positive correlation between D-dimers value and the site of surgery HIV positive cohort **R** = +0.390, $p = 0.049$ and control **R** = + 0.398 $p = 0.03$. The study shows no added effect of HIV in the known risk of major orthopaedic surgery in the development of DVT. Major orthopaedic surgery is a risk in developing DVT as shown in this study by high levels of D-dimers in both groups. Therefore the study recommends a blood test for D-dimers be incorporated in clinical risk assessment tool.

Key Words: Deep Vein Thrombosis, HIV Sero-Positive, HIV Sero-Negative, D-Dimer, Doppler Ultra Sound

DEDICATION

I dedicate this work to my wife Dr. Lena Lambart, for her patience, support and encouragement, my children Alexander, Alisha, Anne and Amari.

"If you think you can, you can. If you think you cannot, you are right"-Mark Twain

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to my supervisor Prof. Yakub. F Mulla for the continuous support of my master of medicine study and research, for his patience, motivation, enthusiasm, and sharing his immense knowledge and experience. His guidance helped me in all the time of research and writing of this dissertation. I would like to thank Dr James Munthali, for his encouragement, insightful comments, hard questions and discussing my ideas with him. My sincere thanks also goes Prof Belington Vwalika for the corrections and advice during the development of my research.

Mr. Salim Patel and Sanket Diagnostic Centre team for facilitation and efficient and reliable running of D-dimer samples.

The Medical Superintendent, The University Teaching Hospital, for permission to carry out my research at the hospital and the Head of Department of Radiology, Dr Veronica Sunkutu-Sichizya for allowing the participants in the study have their Ultrasound scans done. In particular, Mrs. Janet Katanga, Department of Radiology, UTH, for doing the ultrasound scans.

I thank my senior colleagues, Dr Denis Sakala, Dr Jonathan Sitali, Dr James Mulenga and Dr Penelope Machona for the stimulating discussions and constructive feedback. My friends and fellow students Dr Seke Kazuma, Dr Chalwe Mumba, Amon Ngongola and Dr Nelson Banda for the encouragement, support and light moments during the trying times of our training and research.

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ABBREVIATIONS

- DVT: Deep Vein Thrombosis
- VTE: Venous Thromboembolism
- HIV: Human Immunodeficiency Virus
- AIDS: Acquired Immunodeficiency Syndrome
- CD4: Cluster Differential 4
- THR: Total Hip Replacement
- TKR: Total Knee Replacement
- HA: Hemi-arthroplasty
- UTH: University Teaching Hospital

DEFINITIONS

D-dimer: Fibrin degradation Product, a small protein fragment, present in blood after a blood clot is degraded by fibrinolysis

Prevalence: measurement of all individuals affected by the disease(Deep Vein Thrombosis) at a particular time (duration of the study**)**

Prophylaxis: measures designed to preserve health and prevent the spread of disease (Deep Vein Thrombosis)

CHAPTER ONE: INTRODUCTION

1.1 Background

Orthopaedic conditions in HIV seropositive individuals are expected to raise as the life expectancy of those living with HIV improves. It is estimated that 4.2 million people aged 50 and older were living with HIV infection; 2.5 million people being sub-Saharan Africa, accounting for 60% [1] and 71% HIV patients have musculoskeletal as a result of HIV infection, HIV anti-retroviral drugs or both [2]. Deep venous thrombosis has been shown to develop in patients with HIV who are ambulatory and have no known risk factors for pathologic thrombus formation [3]. Severe pulmonary tuberculosis is often complicated by deep vein thrombosis (DVT) because of the association between inflammation and haemostatic changes that can result in an acute phase response and a hypercoagulable state [4]. Although thrombosis has rarely been noted in HIV infected patients before the era of HAART, reports of thrombotic events in such patients is increasing as shown in a case series of 650 patients in the outpatient department 30 (4.6%) developed a total of 43 venous or arterial thrombosis during 1996-2002 [5]. Due to social economic constraints [3] very few patients can afford and thus receive chemical prophylaxis in our local setting.

Major lower limb orthopaedic surgery like hip and knee surgery alone are known to predispose these patients to deep vein thrombosis. Thrombosis is also associated with impaired quality of life, particularly when post-thrombotic syndrome develops [6]. Death occurs within one month of an episode in about 6% of those with deep vein thrombosis and 10% of those with pulmonary embolism [7]. In a prospective study to determine the prevalence of DVT in patients with pelvic, femoral and tibia/fibula fractures at the University Teaching Hospital in Lusaka, it was found that the prevalence of DVT in this population was 10.8% following trauma [8]. This study did not take into account the HIV status of its population and only looked at the prevalence of both asymptomatic and symptomatic DVT in an acute trauma setting. Here lies the challenge in treating HIV positive patients who present with orthopaedic conditions. Surgery of the lower limbs and spine is a major risk factor for the development of thrombosis. There is thus a strong rationale for careful

prospective studies focusing on the prevalence and risk factors involved in the development of thromboembolic complications in patients with AIDS [9].

Since both orthopaedic surgery and HIV infection have been shown to increase the risk of DVT separately, it was postulated that orthopaedic surgery in HIV positive individual would have a synergistic effect on the occurrence of DVT in this population. This study aimed to investigate whether the prevalence of DVT in HIV positive orthopaedic patients is higher compared to HIV negative orthopaedic patients after major surgery. If the prevalence is high, then HIV is an added factor to major orthopaedic surgery in the development of DVT.

1.2 Statement of the Problem

The number of HIV positive orthopaedic patients has increased in the last decade. This is due to improved life expectancy mainly related to increased access to antiretroviral therapy by the general population in Zambia. HIV positive individuals presenting with limb injuries, spine trauma and degenerative diseases undergo major orthopaedic surgery. Major trauma, spine and joint replacement surgery are known risk in the development of DVT.

This study is aimed at investigating the added risk of HIV in the development of DVT after major orthopaedic surgery.

1.3 Study Justification

The HIV positive population is living healthier and more productive lives due to improved access to HAART. With the current drive to start therapy regardless of CD_4 count loose these valuable members of our society due to a preventable post-operative acute deep vein thrombosis is not acceptable. Thus a study whether HIV Status is related to DVT following orthopaedic surgery was warranted.

1.4 Objectives

To investigate whether HIV is an added risk in developing DVT after major orthopaedic surgery.

1.5 Specific objectives

1. To determine the demographic characteristics of acute deep vein thrombosis in HIV sero-positive orthopaedic patients following major surgery.

2. To determine the prevalence of DVT in HIV seropositive individuals undergoing major orthopaedic surgery.

3. To determine the relationship between CD_4 and DVT in HIV seropositive individuals undergoing major orthopaedic surgery.

1.6 Organization of Dissertation

This study is divided into Chapters which are included as follows:

Chapter 1 describes the background, statement of the problem, study justification objectives and specific objectives.

Chapter 2 deals with the literature review explains what Deep Vein Thrombosis, its association with HIV and orthopaedic Surgery, its diagnostic criteria.

Chapter 3 provides the study conceptual framework, research methodology and ethical considerations.

Chapter 4 states the results of the study with illustrations and tables to interpret the data collected.

Chapter 5 discusses the study findings comparing them with local, regional and international literature.

Chapter 6 summarises the study findings, recommendations and study limitations.

CHAPTER TWO: LITERATURE REVIEW

2.1 Deep Vein Thrombosis: Epidemiology and Pathophysiology

Venous thrombo-embolism (VTE) is a physiological derangement resulting in a pathological thrombus or clot formation in the deep venous system [10].Venous thrombosis, comprising deep vein thrombosis and pulmonary embolism, occurs with an incidence of approximately 1 per 1000 annually in adult populations [7]. Rates are slightly higher in men than women, male-to-female ratio is 1.2:1 [11]. Deep venous thrombosis usually affects individuals older than 40 years. The incidence of VTE increases with age in both sexes. The age-standardized incidence of first-time VTE is 1.92 per 1000 person-years and from a demographic viewpoint, Asian and Hispanic populations have a lower risk of venous thromboembolism, whereas whites and blacks have a higher risk, 2.5-4 times higher [11]. There is little information on epidemiology of thrombosis in Africa [7]. Without prophylaxis, patients with a proximal femur fracture have a reported prevalence of fatal pulmonary embolism (PE) as high as 7%. Patients undergoing elective THA and TKA have been described as having rates of symptomatic PE without prophylaxis of up to 20% and 8%, respectively [12].

A process called homeostasis maintains the blood vessel wall integrity as well as intravascular pressure and osmolality within certain physiological ranges to maintain blood in its liquid and clot-free state until such a time as injury necessitates clot formation [10]. When dysregulation of the balance between prothrombin and antithrombotic state occurs pathologic thrombus formation occurs. Three conditions must be met for one to develop deep vein thrombosis as describe by Virchow in 1856 namely, stasis (alteration of blood flow), vascular endothelial injury (damage to the vessel wall) and hypercoagulability (alteration in the constituents of blood) [13]. These primary influences that predispose to thrombus formation are called Virchow’s triad. It is important to note that endothelium does not need to be denuded or physically disrupted to contribute to the development of thrombosis; any perturbation in the dynamic balance of pro-thrombotic and antithrombotic effects can influence local clotting events [10].

2.2 Deep Vein Thrombosis Clinical Features

Symptoms of deep venous thrombosis (DVT) may include, oedema (most specific symptom), Leg pain (occurs in 50% of patients but is nonspecific), tenderness (occurs in 75% of patients), warmth or erythema of the skin over the area of thrombosis and clinical symptoms of pulmonary embolism (PE) as the primary manifestation [11]. The physical findings in DVT may include: calf pain on dorsiflexion of the foot (Homans sign); palpable, indurated, cordlike, tender; subcutaneous venous segment; variable discoloration of the lower extremity and blanched appearance of the leg because of oedema [11].

2.3 Deep Vein Thrombosis: Risk Factors

An understanding of the risk factors for venous thrombosis is necessary in order to maximize the prevention of this disease in high risk individuals and groups of patients. The major risk factors for thrombosis include endogenous patient characteristics such as obesity and genetic factors, and triggering factors such as surgery, immobility or pregnancy [7]. Some of the risk factors are modifiable, while others, like advancing age and genetic predispositions, are not. Venous thrombosis tends to occur due to the additive effects of endogenous, genetic and environmental risk factors present simultaneously [14]. A study followed 21,680 people looking for occurrence of venous thrombosis in the general population over 7.6 years demonstrated that about one-half of all thrombosis events were considered secondary to triggering factors(in 52%, cancer in 48% and surgery in 42%) and, among these, 65% of the time more than one triggering risk factor was present [7].

Deep vein thrombosis develops in 50–60% of patients undergoing elective hip replacement without prophylaxis and fatal pulmonary embolism occurs in 1–5% [15]. Orthopaedic surgery is a well-known risk factor for deep vein thrombosis. Without thrombo-prophylaxis, the incidence of venographically detected DVT is 42.0%–57.0%, and that of PE is 0.9%–28.0% after total hip arthroplasty [16]. The release of thromboplastin from the dissected soft tissue and reamed bone, as well as venous stasis during surgery and postoperative immobility, are responsible for high rates of deep vein thrombosis [17].

2.4 Deep Vein Thrombosis in HIV

\Human Immunodeficiency Virus seropositive patients can present with a number of orthopaedic disease manifestations that may require surgical intervention.

Surgery of seropositive patients presents with its own complications. Various abnormalities predisposing to a hyper-coagulable state have also been reported in AIDS patients including the presence of antiphospholipid antibodies and the lupus anticoagulant; deficiencies of protein C, protein S, heparin cofactor II, and antithrombin and increased levels of von Willebrand factor, and d-dimers [18]. These abnormalities correlate with the severity of HIV-associated immunosuppression as measured by the CD_4 cell counts and with the presence of concurrent infectious or neoplastic diseases [9]. A retrospective study of active HIV patients at a large U.S. clinic to evaluate the incidence of VTEs during the HAART era (January 1, 1996 to June 30, 2007) showed an incidence of deep venous thromboembolism of 377 cases/100,000 person years [19]. When compared to age-matched males in the general population, HIV positive persons in this study had a fourfold higher rate of deep vein thromboembolism with a median age at venous thromboembolism of 36 years (range, 27–68). Patients with a thrombosis compared to those without had significantly lower current CD_4 (153 versus 520 cells/mm, (p _ 0.001) and nadir (76 versus 276 cells/mm3, p _ 0.001) CD_4 counts, and 59% were receiving HAART. Another retrospective study from the University of Connecticut Health Centre [20] found 7.6% (10 of 131) HIV-infected patients with an unexplained DVT or pulmonary embolism occurring at CD_4 counts less than 200/mm, and in patients with the concurrent presence of opportunistic infections or acquired immunodeficiency syndrome (AIDS)-related neoplasms.

Studies into deep vein thrombosis in surgical patients with HIV co-infection are limited but a retrospective review of HIV/AIDS-infected patients with DVT admitted to Mount Sinai School of Medicine/Cabrini Hospital in New York over a five period 5 years (1995 to 2000) showed of those admitted to the hospital 45 (0.95%) were found to have DVT [18]. There were 36 males and nine females (mean age 43 years) in which 38 had infectious complications and 13 developed a malignancy. The distribution of thrombosis were: the femoral vein in 23 patients, the popliteal vein in 20 patients, and the ilio-femoral system in 2 patients. Twelve patients had recurrent DVT and three patients developed a pulmonary embolism. HIV/AIDS infection was found to be considerable risk for development of DVT in the lower extremity. Statistically DVT in HIV/AIDS was approximately 10 times

greater than in the general population. Emphasis upon prevention and vigorous treatment of DVT was recommended [18].

2.5 Deep Vein Thrombosis in Orthopaedics

The incidence of asymptomatic DVT after a major orthopaedic surgery without prophylaxis reportedly ranges from 30% to 80%, whereas the incidence of symptomatic DVT reportedly ranges from 0.5% to 4% [16]. In 2014 a prospective study to determine the prevalence of DVT in patients with pelvic, femoral and tibia/fibula fractures at the University Teaching Hospital Lusaka found of 74 patients 10.8% developed deep vein thrombosis with no correlation between the severity of the injury and the development of DVT [8]. No particular risk factor was identified to increase the risk of DVT in trauma patients in this study. The study only looked at patients that had trauma and did not consider surgical intervention or HIV sero-status.

In a recent analysis of a nationwide claim registry in China of incidence of deep vein thrombosis after major lower limb orthopaedic surgery concluded that among major lower limb surgeries, advanced age, female gender, and undergoing a knee replacement arthroplasty were found to be risk factors for developing postoperative DVT [21]. These findings further emphasize the need for orthopaedic surgeons to consider the development of DVT after surgery in high-risk patients

2.6 HIV in Orthopaedics

Of 101 HIV patients studied by Berman et al 71% had musculoskeletal manifestations during the course of their disease [2]. These included, musculoskeletal infections, Avascular Necrosis, Reduced bone density and inflammatory conditions. Orthopaedic manifestations in HIV patients may be directly caused by the HIV infection, drugs used in the treatment of HIV or both HIV infection and its treatment [2].

A high incidence of HIV-positive patients presenting for elective and emergency surgery could be expected in pandemic areas [22]. 24% of patients admitted for surgery at Lusaka's University Teaching Hospital in 1990 were HIV-positive [23] . Currently the prevalence rate of HIV in Zambia of adults between the ages 15-49 is 14.3 % [1]. In a study of 76 patients, found that 16% of their patients admitted for orthopaedic procedures were HIV-positive [24]. There are several bone and joint

conditions which have to be considered in HIV-positive patients: Trauma, degenerative bone and joint conditions like avascular necrosis, bone infections like osteomyelitis and tumours like non-Hodgkin's lymphoma.

While degenerative osteoarthritis is not common in the young HIV-positive patients, inflammatory arthroplasty and osteonecrosis (AVN) are common [22]. The incidence of AVN of the femoral head in HIV-positive patients has been reported to be 0.45%, which is 45 times greater than in normal populations. Patients who are HIV-positive have an increased prevalence of predisposing factors to AVN such as protease inhibitors use with associated hyperlipidaemia HIV-positive patients may need a hip arthroplasty for AVN, severe arthroplasty, or even degenerative arthritis [25].

The prevalence of osteoporosis in HIV-infected individuals is more than three times greater compared with HIV-uninfected controls. ART-exposed and PI-exposed individuals had a higher prevalence of reduced Bone Mineral Deposits and osteoporosis compared with their respective controls [22]. This may predispose these individuals to fractures and the need for orthopaedic surgery. The risk of fracture in men and women with HIV found similar rates [26]. All these conditions highlighted may require orthopaedic surgical intervention.

In Malawi a short-term follow-up, functional outcome and incidence of early and late infection after total hip replacement (THR) in a group of HIV-positive patients who do not suffer from haemophilia or have a history of intravenous drug use concluded that it was safe to perform THR in these patients [27]. No revision procedures had been undertaken in any of the patients, and none had any symptoms consistent with aseptic loosening. However the study did not look into the prevalence of DVT in their study population.

No studies have investigated HIV as an added risk factor to major orthopaedic surgery in the development of DVT. Thus there is a gap in knowledge in this area and with the higher numbers of sero positive patients requiring orthopaedic surgery it is important to investigate this aspect HIV continuum of care.

2.7 Diagnosis of DVT

Most thromboembolic events after elective orthopaedic surgery are reported to develop during the first postoperative week [28]. The American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines on antithrombotic therapy and prevention of thrombosis (9th Edition) say that objective testing for DVT is crucial because clinical assessment alone is unreliable, and the consequences of misdiagnosis are serious, including fatal pulmonary embolism. Although anticoagulant therapy is effective, unnecessary use entails expense, inconvenience, and risk of major haemorrhage. Only a minority of patients evaluated for suspected DVT actually have the disease. Therefore, diagnostic strategies must be able to correctly rule in DVT when it is present and safely rule out DVT when it is absent. Three categories of tests are typically used to determine the probability of DVT; (1) clinical probability assessment based on patient history and clinical findings, (2) D-dimer assays, and (3) imaging studies (most commonly venous ultrasonography and less frequently venography), CT scan, or MRI. Diagnostic Testing often requires that the results of more than one assessment are combined [29]. High plasma D-dimer level is a moderately sensitive, but less specific marker in the detection of early of DVT after TKA. Measurement of serum D-dimer alone is not accurate enough to detect DVT after TKA. Venography is recommended in patients with elevated D-dimer and clinically suspected but asymptomatic DVT after TKA [21].

CHAPTER THREE: METHODOLOGY

3.1 Conceptual Frame Work of Study:

Ethical approval was sought from the University of Zambia Biomedical Research Ethics Committee prior to commencement and enrolment for the study. Written informed consent was obtained before any participants were enrolled by signature or witnessed thumb print. The flow of progression of the patient in the study is shown in Figure 3.1, and with the use of the data collection tool shown in Appendix 1, the patient's demographics, HIV status, ART treatment, surgical history and surgery planed were obtained. This tool was designed to ensure the patients recruited met the inclusion criteria outlined in Table 1.

A blood sample was take on the second to their day following and the details of the surgery were recorded in the post-operative data collection tool including the D-dimer results. Those that were found to have positive D dimer and clinical signs of DVT then went on to have Doppler ultrasound done in their lower limbs to confirm the presence or absence of obstruction in their venous system.

The D-dimer were tested using the VIDAS© D-Dimer Exclusion II® as outlined in Appendix 2.

The study did not interfere with treatment plans of the attending surgical teams but results of D-dimers and Doppler ultrasound were made available to the attending teams as DVT is a life threatening condition. Patients were free to opt-out anytime during the course of the study and any information collected from them was not used in the study unless expressed permission was given by the patient.

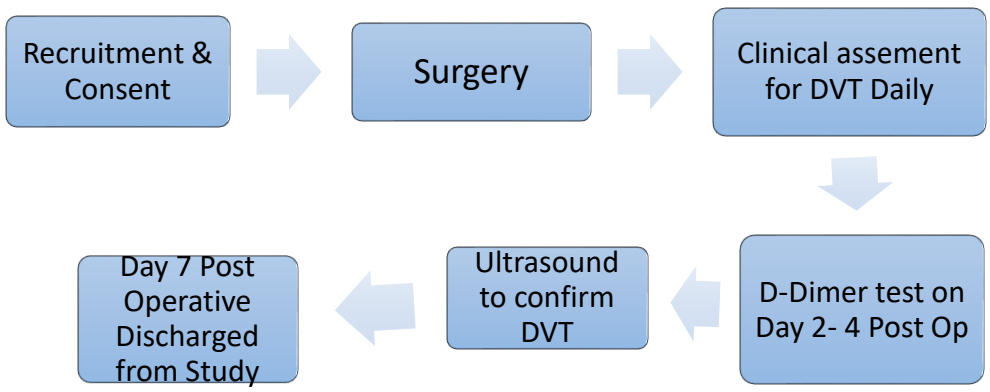

Figure 3.1 Conceptual Frame Work

3.2 Methodology

This was a cross sectional study conducted at the University Teaching Adult Hospital a tertiary level hospital in Lusaka Zambia which also serves as a National Referral Centre. Convenience sampling patients was done for those undergoing major limb and spinal orthopaedic surgery who met the inclusion criteria as outlined in Table. 1, were enrolled in the study. The sample size was calculated using the prevalence formula as shown in Table 2 with each sample size formula shown in Table 3.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria:	Exclusion Criteria:
Age 21 years or above, Male or Female	Patients with known malignancies
Planned for elective major lower limb and spinal orthopaedic surgery: Intramedullary Nailing, Total and Partial Hip Replacements, Knee Replacement, Plating and Screw Fixation of Fractures, Open Join reduction, Arthrodesis, and sequestrectomies	Patients on hormone replacement therapy
Irrespective of HIV status	Patients on pro-coagulant therapy
Any CD4 Count	Patients with prior history of DVT or PE
On ART or not	Patients who are pregnant

Study Site: University Teaching Hospital, Lusaka, Zambia.

Type of Study: Cross Sectional Study

Target Population: Patients undergoing major orthopaedic surgery

Study Population: Patients undergoing major lower limb and spinal orthopaedic surgery who meet the eligibility criteria

Sampling method: Convenient Sampling will be used

Sample size calculation was done using *Open Epi* as below:

Sample Size: 50 patients at 80% power

Sample size was calculated using the formula: $N = [Z^2 \times P(1-P)] / E^2$

N = Sample required,

Z = Z statistic for a given level of confidence = 1.282 when using a 95% CI

P = being 0.42as 42% is the expected percentage

E = confidence interval, usually 0.05= this refers to the accuracy range (+/-5)

Table 2: Table Sample Size Calculation Variables

Sample Size: X-Sectional, Cohort, & Randomized Clinical Trials	
Two-sided significance level (1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	5
Percent of Exposed with Outcome	42
Odds Ratio:	14
Risk/Prevalence Ratio:	8.4
Risk/Prevalence difference	37

Table 3: Samples Sizes Explained

	Kelsey	Fleiss	Fleiss with CC
Sample Size – Exposed	21	20	25
Sample Size-Non-exposed	21	20	25
Total sample size:	42	40	50

Data Analysis, Charts and Tables: were done using *SPSS version 23* and results shown in next chapter.

3.3 Ethical Considerations

Ethical approval was sought from the University of Zambia Biomedical Research Ethics Committee prior to commencement and enrolment for the study.

All participants enrolled had the study explained to them and information sheet about the study was provided in both English and Chi Nyanja. Those that were unable to read English or Chi Nyanja had it read to them by a research assistant. Written informed consent was obtained before any participants were enrolled. Thus a signature or thumb print was used to affirm participation in the study.

All the information obtained from the participants was kept with strict confidentiality and was used solely for the purpose of the research and only relevant medical personnel were made aware of any apparent medical conditions of the patients that became apparent during the study. All the information is kept under lock and key and only the researcher and data analysis team have access to it.

Patients were free to opt-out anytime during the course of the study and any information collected from them was not used in the study unless expressed permission was given by the patient.

CHAPTER FOUR: RESULTS

5.1 Demographics

A total of 42 consented participants were enrolled in the study after. The sampling was convenient, recruiting all patients booked elective major lower limb surgery or spinal surgery over a period of 4 months from January 2017 to April 2017. Fifty-four percent of the patients (n=23) were HIV negative and 46 % (n=19) were HIV positive. The gender distribution was 81% (n=34) male of which 41% (n=14) were HIV positive as shown in figure 5.1. Nineteen percent of the patients (n=8) were female of whom 62 %(n=5) were HIV positive**.** The majority (40.5%) of the study population between the ages of 21 and 30 with 82% of the total population being below the age of 50 years as shown in figure 5.2.

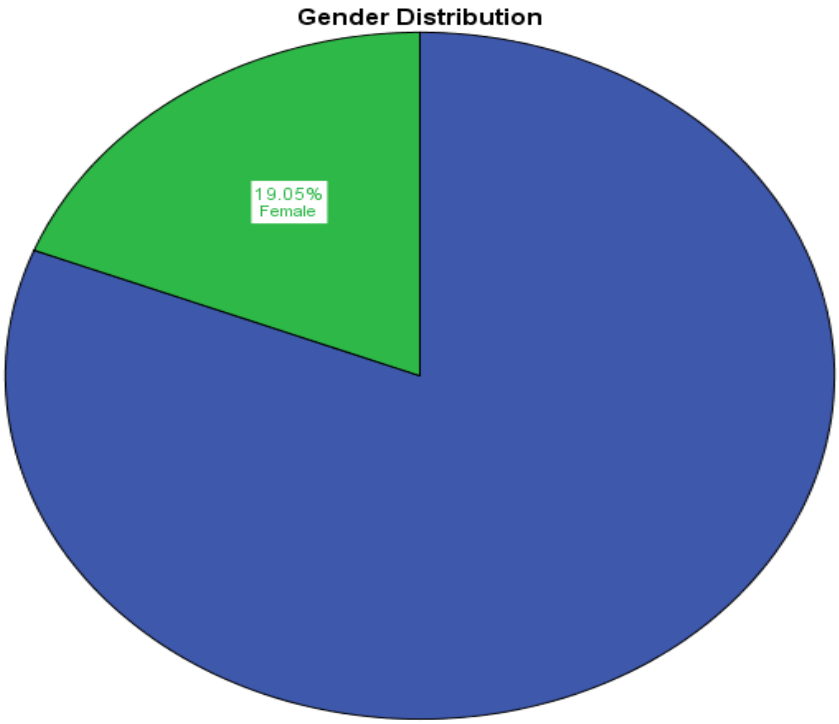

Figure 5.1: Gender Distribution

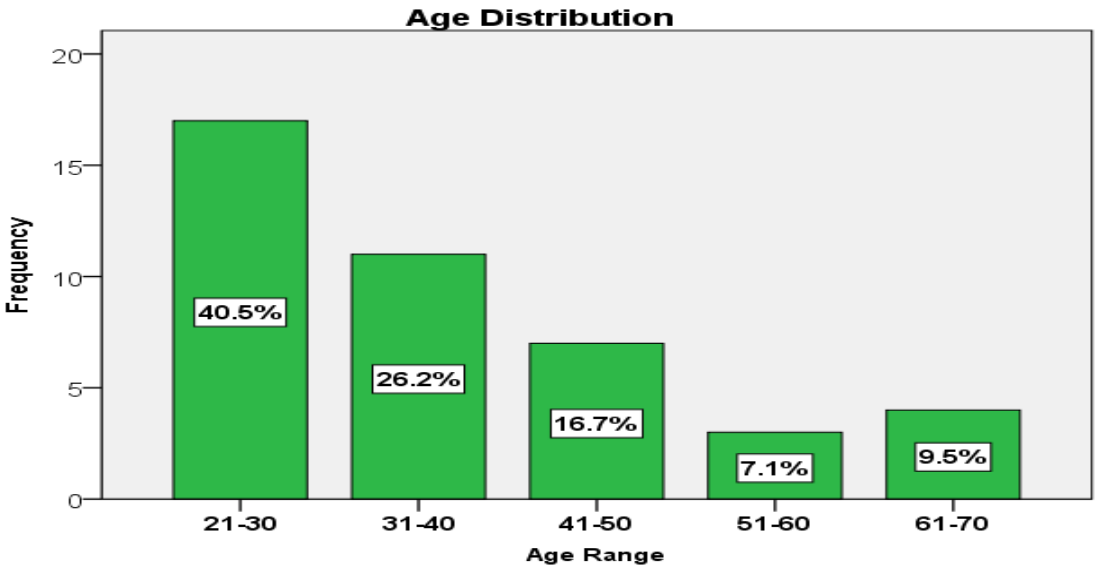

Figure 5.2: Age Distribution

5.2 HIV and Surgery Site

The trend continued when the age distribution in the two arms of the study was analyzed with 84% of the HIV positive and 82% of the HIV negative falling below the age of 50 years shown in figure 5.3 below:

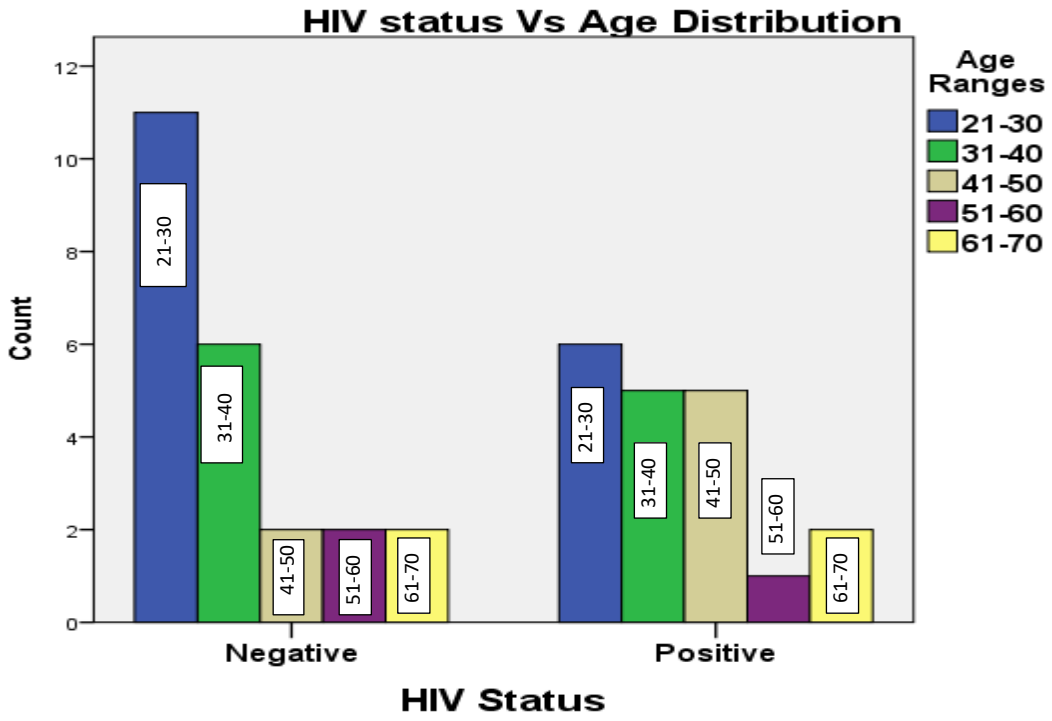

Figure 5.3: Age and HIV Status

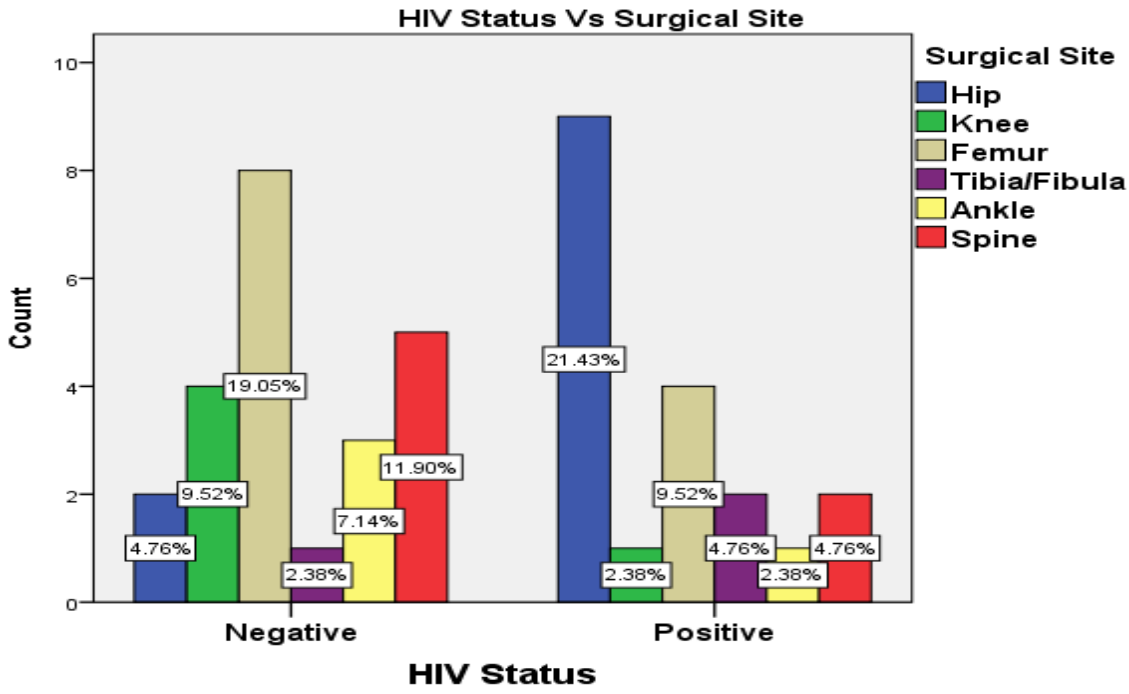

Figure 5.4: Site of Surgery and HIV Status

The ages were almost evenly distributed in the HIV positive cohort below 50 years unlike that of the HIV negative cohort which had an age distribution skewed towards the 21-30 age range as shown above in Figure 5.4.

When the site of surgery and age were analyzed in this study it was found that femur and knee surgery site was more common in 21-30 age range whereas hip surgery site was more common in 41-50 age range with the spinal surgery site being more common in the 31-40 age range as shown in Figure 5.5 below

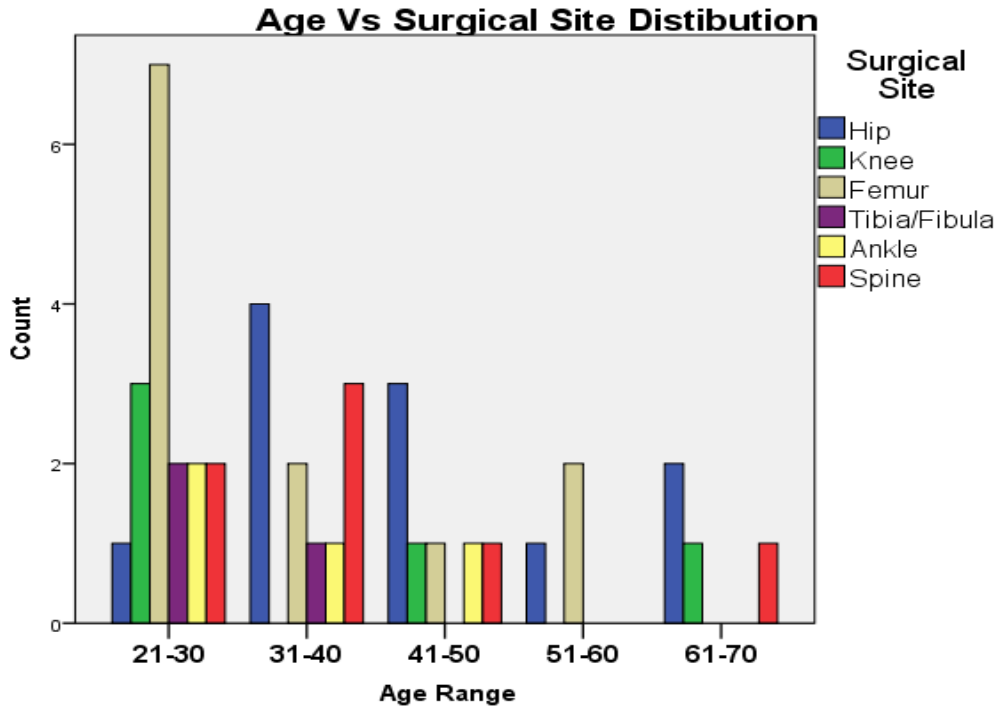

Figure 5.5: Age and Type of Surgery

The gender distribution was 81% (n=34) male with a breakdown of 41% (n=14) being male HIV positive and 59% (n= 20) HIV negative. The males most common surgery being the femur followed by hip surgery as compared to the females having hip surgery as their most common type of surgery as shown in the Figure 5.6 below.

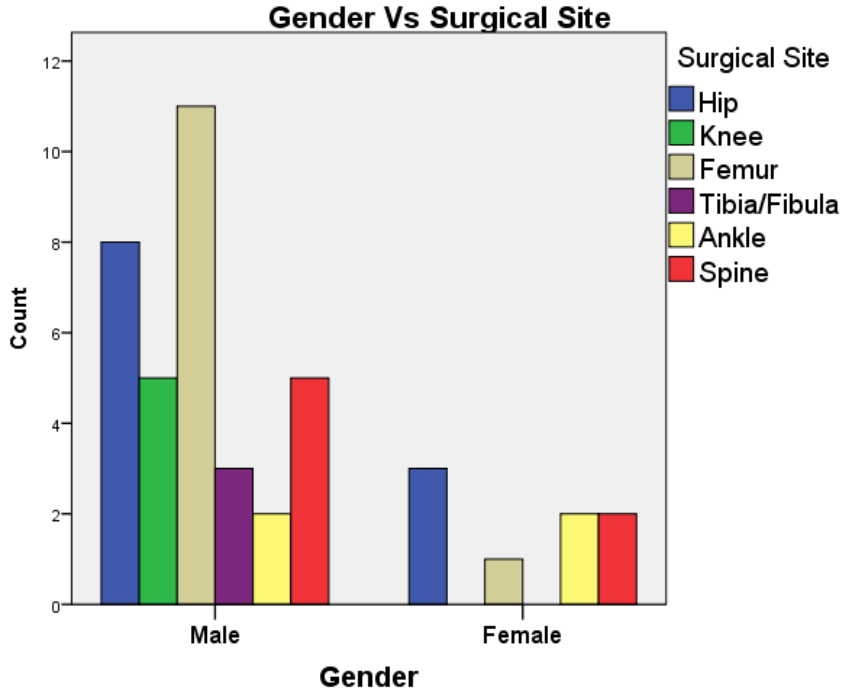

Figure 5.6: Gender to Site of Surgery

73% (14) of the HIV positive cohort had a CD_4 count between 200 and 500 cells per microliter and the remainder (27%) had CD_4 count above 500 cells per microliter and none had a CD_4 less than 200 cells per microliter. Of these 79% were on antiretroviral therapy distributed in the Figure 5.7 below:

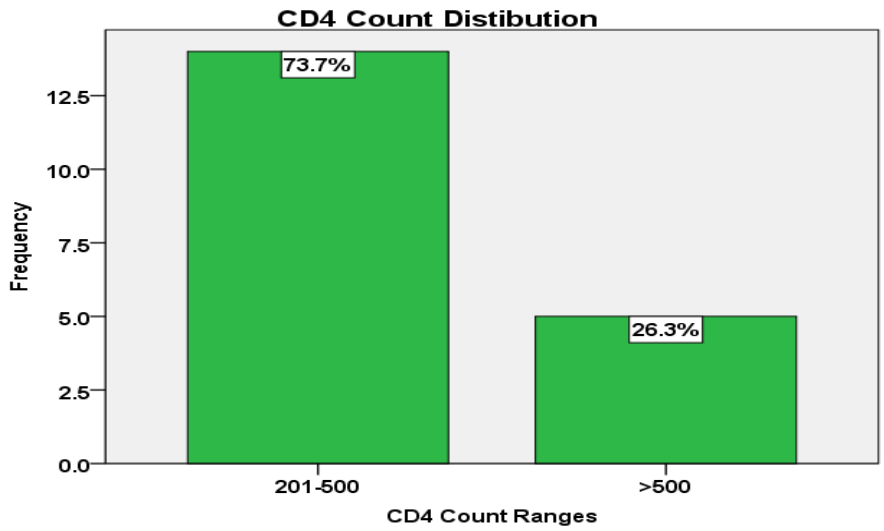

Figure 5.7: Percentage Distribution 0f CD4 Count Ranges

The majority (60%) of those on antiretroviral therapy had been taking the medication for more than 3 years as shown in Figure 5.8 below:

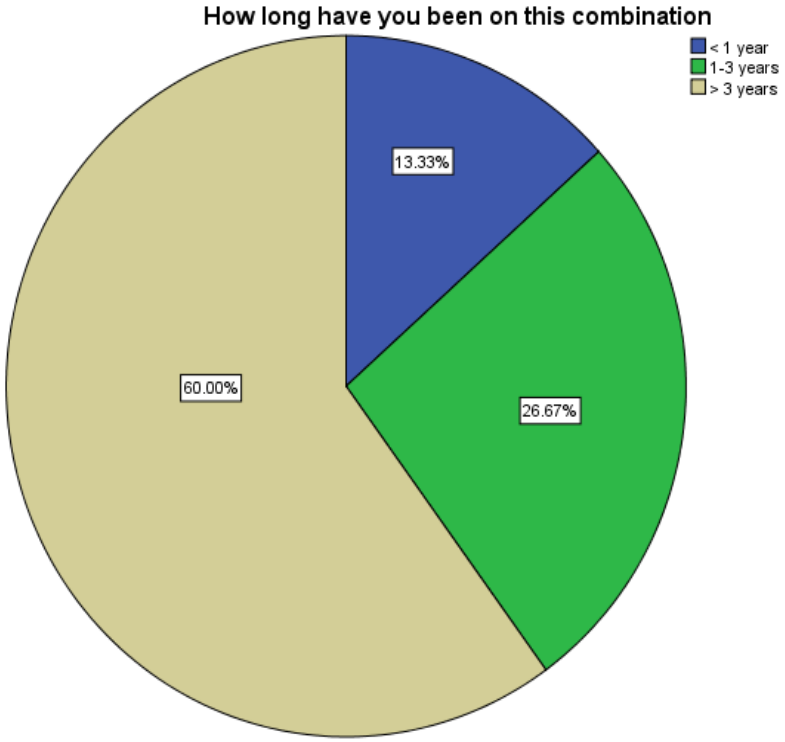

Figure 5.8: Percentage on ART

5.3 DVT and HIV

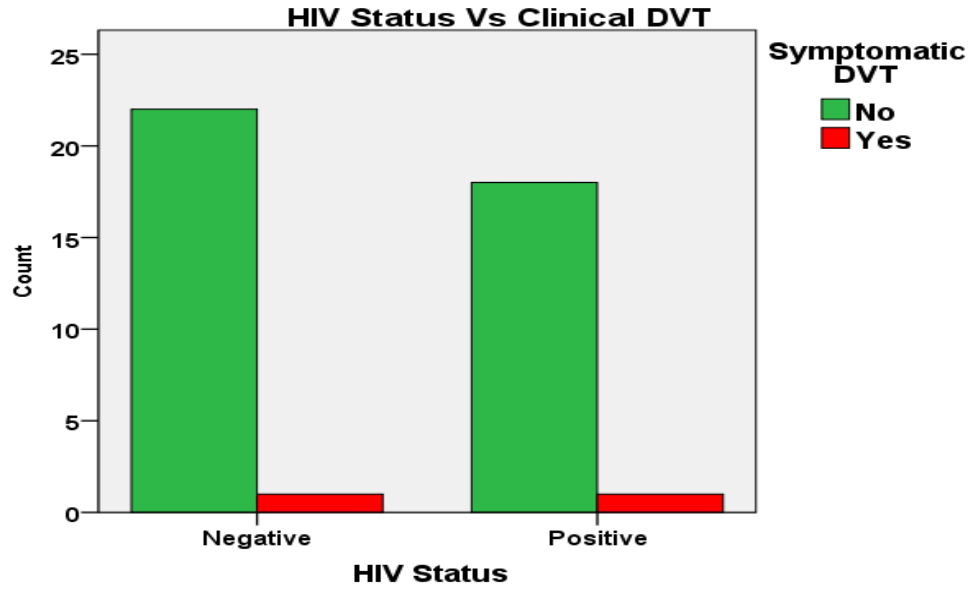

Figure 5.9: Number of Symptomatic DVT

Only 1 patient in each of the cohorts developed clinical and ultra sound confirmed DVT which gave a prevalence of 5.3% in the HIV positive group and 4.3% in the control arm who were HIV negative as shown in Figure 5.9. The chi-square test (Table 4 and Table 5 below) was employed to test if there was a significant difference in the occurrence of clinical DVT in the two groups and it was found that there was no difference at X^2 0.019 p= 0.890. Significance was further tested using the Mantel – Haenzsel test and still found to X^2 0.339 p= 0.560 in Table 6 below. *Thus the null hypothesis was accepted***.**

Table 4: Cross Tabulation

Cross Tabulation of HIV Status and Clinical Confirmed DVT

			Did the patient develop any clinical signs of DVT?		
			No	Yes	Total
What is the HIV Status in the last 3 Months	Negative	Count	22	1	23
		Expected Count	21.9	1.1	23.0
	Positive	Count	18	1	19
		Expected Count	18.1	.9	19.0
Total		Count	40	2	42
		Expected Count	40.0	2.0	42.0

Table 5: Chi-Square Test

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.019[a]	1	.890		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.019	1	.890		
Fisher's Exact Test				1.000	.706
Linear-by-Linear Association	.019	1	.891		
N of Valid Cases	42				

Table 6: Tests of Conditional Independence

Tests of Conditional Independence

	Chi-Squared	Df	Asymptotic Significance (2-sided)
Cochran's	.019	1	.890
Mantel-Haenszel	.339	1	.560

The prevalence of positive D-dimer test was 94.7% (n=19) for the HIV positive group and 95.6% (n=22) for the HIV negative group as shown in figure 5.10 below. The Pearson Chi Square was applied gave $X^2 = 0.19$ $p = 0.890$ meaning there was no significant difference between the two groups. As with the DVT comparisons this means that there was no difference in the occurrence of a positive D-dimer value whether HIV positive or negative.

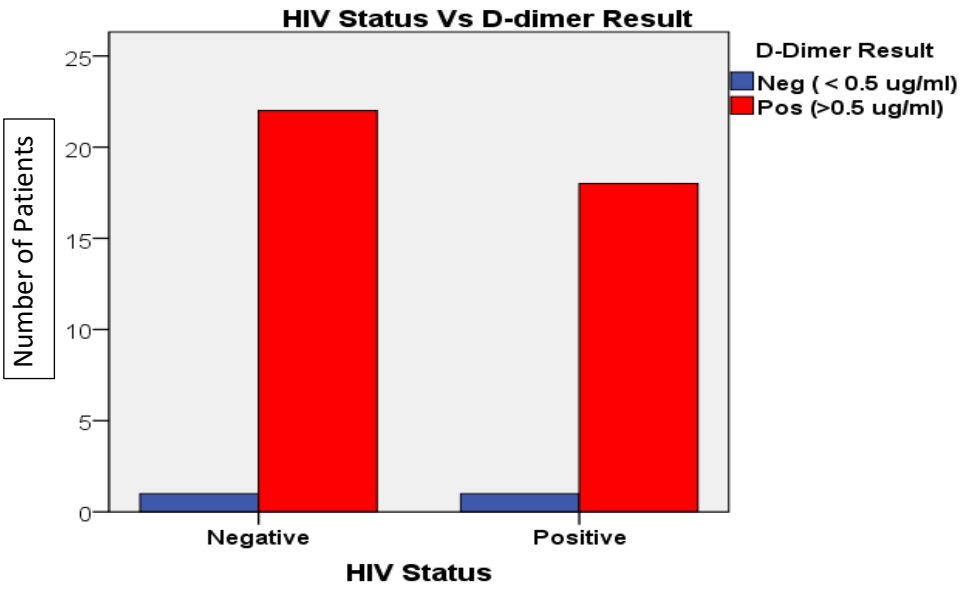

Figure 5.10: Number of Patients per D-dimer Count.

There is a positive correlation between the type of surgery done and increasing value of the D-dimers that is the more proximal the surgery was the higher the value of the D-dimer. For the HIV positive cohort the **R** = +0.390, *p = 0.049* and **R** = + 0.398 *p = 0.03* for the control. As shown in Figure 5.11, The majority of the D-dimer values for the Hip and Knee surgeries were both above 2.00 ug/ml while for the femur surgeries the higher values were in those that were HIV negative. For the spine surgeries the majority of the values were below 2 ug/ml with one outlier of 5.39 ug/ml which was in a HIV negative cohort. The HIV positive patients with CD_4 count 200-500 cell/ul had a wider range of D-dimer values from 0.95-5.50 ul/ml, whereas the those with greater than CD4 count 500 cell/ul had a narrower range of 0.28 to 3.87ug/ml as Figure 5.12 shows below.

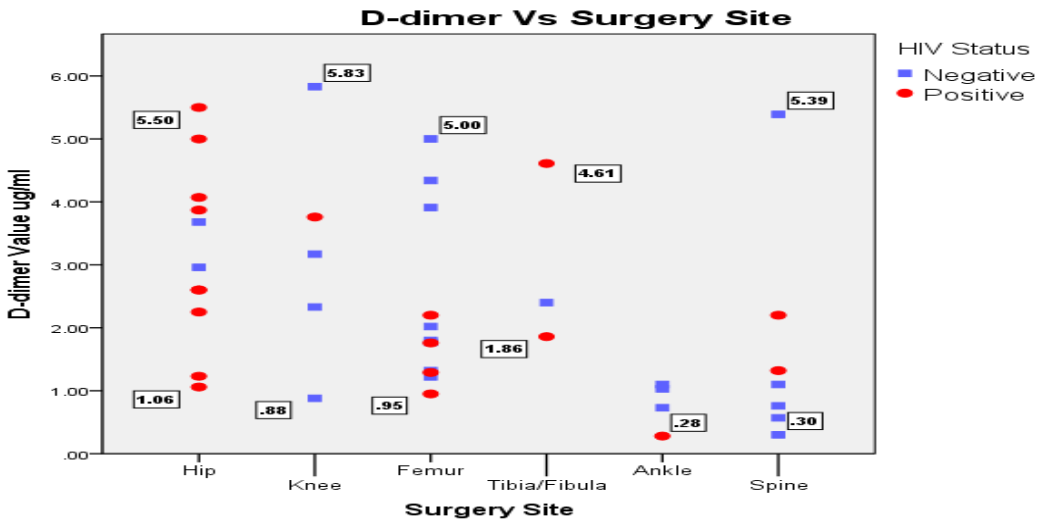

Figure 5.11: D-dimer against site of surgery

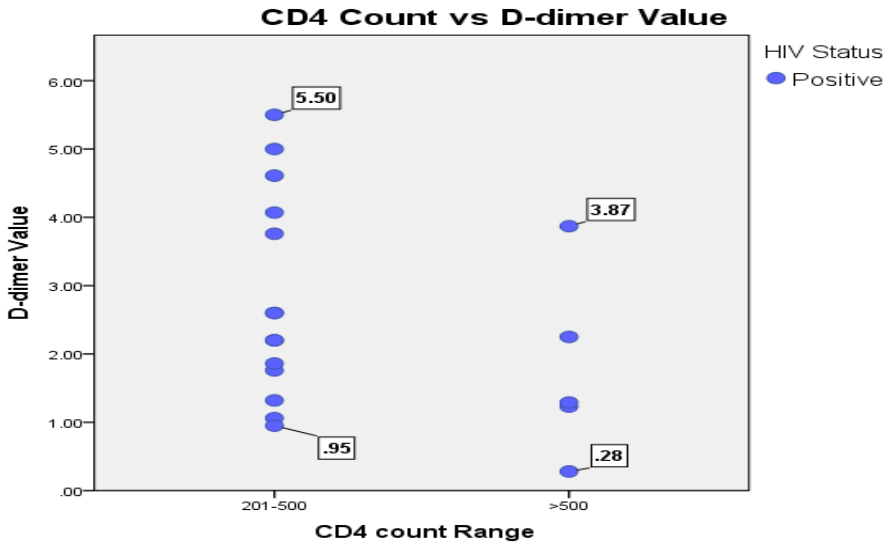

Figure 5.12: D-dimer against CD count ranges

There was 35.7% of the surgeries lasting between 1 and 2 hours where as 47.6% between 2 and 3 hrs with only 16.7 % lasting more than 3 hours. There was no correlation between the duration of surgery and the values of the D-dimers. Only 1 patient whose surgery took more than 3 hours had a very high value above 5 ug/ml as shown below

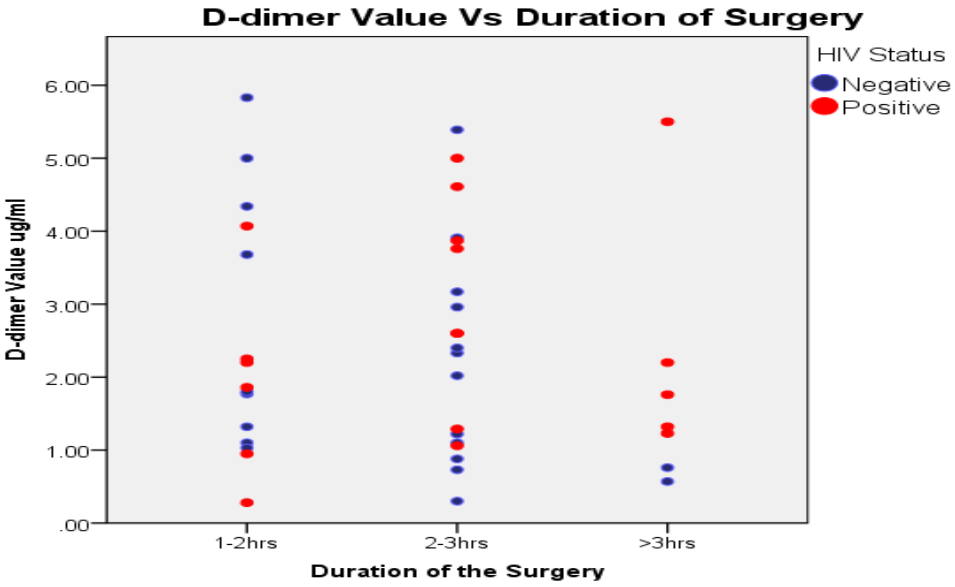

Figure 5.13: D-Dimer against Duration of Surgery

The majority of those on ART were on ®Atripla (a fixed dose combination containing efavirenz, emtricitabine and tenofovir disoproxil fumarate) with a wide range of D-dimer values however the high values were seen in both those on ART and not on ART in Figure 5.14. There was a positive correlation of the duration of ART and the high D-dimer values as shown in Figure 5.15 below.

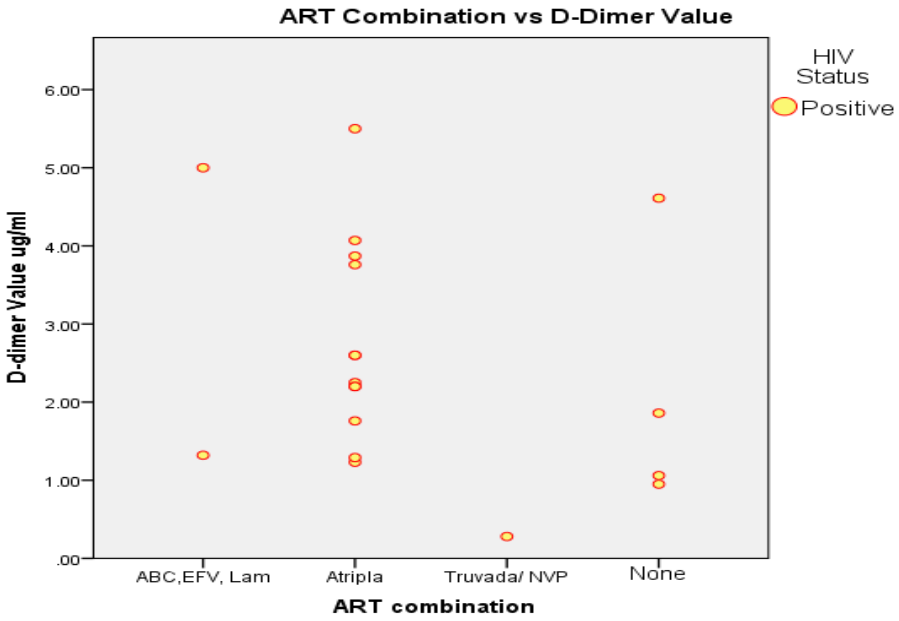

Figure 5:14 D-Dimer per ART Combination

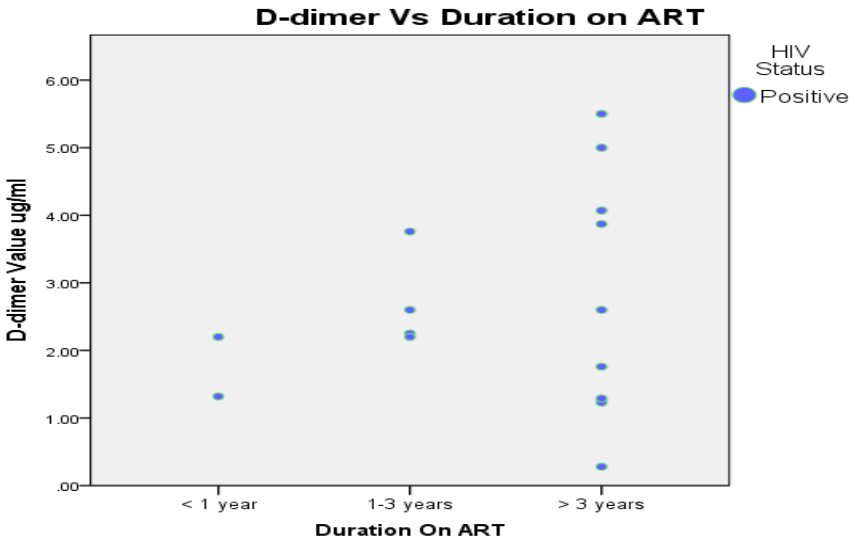

Figure 5.15: D-Dimer against Duration ART

Table 7 below summaries the main statistical values calculated using *SPSS ver.23* from the data collected.

Table 7: Summary of Statistics

Statistics	*HIV(+)*	*HIV(-)*
Mean D-dimer:	**2.55** +/- 1.50 µg/ml	**2.33** +/- 1.65 µg/ml
Prevalence – D-dimer Positive	94.7%	95.7% (X^2 0.019 *p=0.89)*
Correlation of D dimer value Vs Surgery Site	R +0.390 *p = 0.049*	R+ 0.398 *p = 0.03*
Prevalence of Clinical DVT: No difference	5.3 %	4.3% (X^2 0.019 *p= 0.89*)
No difference in D-dimer Positive Result among CD_4 count ranges (X^2 = 2.95 (p=0.89)		
CD_4 Count Ranges	**200-500 cell/ul**	**>500 cells/ul**
D-dimer Range	1.06- 5.50 ug/ml	1.23- 3.80 ug/ml

CHAPTER FIVE: DISCUSSION

The null hypothesis proposed that there was no difference in the prevalence of acute deep vein thrombosis in HIV seropositive orthopedic patients following major surgery at the University Teaching Hospital, Lusaka. The risk factor investigated was the HIV status of the patients, having been exposed to major orthopedic surgery with the outcome being whether they developed of DVT. The study showed that the patients that were HIV positive had no added risk in the development of DVT compared to their HIV negative counterparts following similar orthopedic surgery. This is despite the findings of Mundama et al who found that HIV positive individuals were at higher risk of developing DVT in the medical wards [3]. The study has not disapproved their findings but suggests that orthopedic surgery equalizes the risk for development of DVT in both populations. In the study by Chibeza et al, clinically symptomatic and confirmed DVT was 1.4% and in Mundama et al it was 1.7 % while their asymptomatic prevalence was 9.45% and 9.43% both of which were very similar [8] [3]. Of note however the prevalence of symptomatic DVT in this study was 5.3% in the HIV positive group and 4.3% in the HIV negative group, statistically no significant difference between the two (X2 0.19 p = 0.89). This is similar to the values (0.5%-4%) proposed for symptomatic DVT in patients who have not received prior chemoprophylaxis, as did the patients in our study, proposed by Falck-Ytter et al in American College of Chest Physicians Evidence-Based Clinical Practice Guidelines of 2012 [12]. This implies that an HIV positive patient who has undergone lower limb surgery is three times more likely to develop DVT than an HIV positive patient admitted to the medical ward. Both patients that developed symptomatic DVT had similar operating times and were of an elderly age group. It is postulated from our study that major orthopedic surgery is such a potent risk factor that is masks the effects of HIV as a risk factor in the development of DVT. Thus HIV should be considered as a risk factor in the development of DVT as supported by the literature review, but it is just not a significant factor in orthopedic patients undergoing major surgery.

The prevalence of a positive D-dimer test result (> 0.5 ug/ml) was 94.7 % for the exposed group and 95.6 % for the control group with no significant difference in the two groups. D-dimer values are expected to be high following surgery as a result of

the fibrinolysis of the clots that occurs following tissue dissection [13]. This increased levels of circulating degradation products places the patient in a hypercoagulable state. In the study by Chung-Jen et al to detect early DVT after total knee arthroplasty, high D-dimer level greater than 2.0 μg/ml showed 68% sensitivity, 55% specificity, 60% accuracy, 50% positive predictive rate and 72% negative predictive rate [21]. Positive D-dimer values obtained in our study ranged from 0.57 ug/ml to 5.39ug/ml, similar mean values of 2.33 +/- 1.65ug/ml in the control and 2.55 +/- 1.50ug/ml in the HIV positive group. Thus a high number of these patients had a 50% chance of developing DVT when using the positive predictive value from the Cheng et al study. Doppler ultrasound has a far better sensitivity in detecting asymptomatic DVT [29] and thus a better screening tool. In this study the D-dimer values were used to estimate the risk potential of the patients developing DVT rather than a screening tool.

Those that were HIV positive and underwent hip surgery the D-dimer values had a wide distribution from 1 ug/ml to 5.37ug/ml compared to the control group which was narrow at 3ug/ml to 3.8ug/ml. The situation was reversed with those that had femur surgery in which in the control group range was wide from 1.2ug/ml to 5.0ug/ml compared to the exposed group whose range was narrow at 1ug/ml to 2.2ug/ml. Comparing femur and hip surgery in both cohorts showed a wider range and higher values in the HIV positive group. The patient distribution for type of surgery should have been matched in terms of numbers, age and sex so as to compare the ranges of the D-dimer values. Significant correlation was found between the D-dimer value and the type of surgery done, with the HIV positive group giving an R +0.390 (***p = 0.049***) and that of the control was R +0.398 ***(p = 0.03***). Thus the hip, knee and femur surgeries had more D-dimer values clustered above value of 2ug/ml as compared to that of the tibia, ankle and spine surgeries whose clusters were below 2ug/ml. Proximal limb surgeries gave higher values of D-dimer than that of distal limb surgeries likely due to the fact that they involved more tissue dissection and intimal blood vessel injury as a result of joint manipulation. This is similar to the Chung-Jen's finding for high D-dimer values for knees replacement surgery's their study [21].

The relationship between CD4 count and D-dimer values from the literature review suggests that lower CD4 counts would predispose the patients D-dimers and hence

DVT. None of the patients recruited in this study had CD4 less than 200 cells/ul can because most patients with CD4 below this value had their elective surgeries delayed until their CD4 count had improved to avoid prosthetic infections. Treatment of patients with HAART and optimization of underlying comorbidities appears to lower the rate of prosthetic joint infection in this patient population [30]. Statistically there was no difference in the occurrence of a positive D-dimer value ($\boldsymbol{X^2}$ 2.95, $\boldsymbol{p = 0.89}$) in between the two CD4 ranges. It is has been shown that higher CD4 counts were associated with less morbidity [31] and analysis of the values of the positive D-dimers showed the patients that had CD4 of more than 500 cells/ul had values ranging from 1.23 to 2.25 compared to a range of 0.95 to 5.00ug/ml in those with CD4 between 200-500 cells/ul. It can be inferred that less fibrin degradation products were produced postoperatively in patients with higher CD4 counts but both had high D-dimer values.

The gender distribution in our study was skewed towards the male gender at 81%. A similar to trend was seen in a study to determine the prevalence of Trauma cases and adoption of the Kampala Trauma Score at the University Teaching Hospital in which males age younger than 50 years made up the majority of trauma. [32]

In both cohorts 80 % of patients were younger than the age of 50 years as most of the surgeries were done for lower limb trauma. These are high energy injuries which tend to occur in a younger age group. As outlined by Govender et al degenerative hip pathologies are seen in the younger age group in HIV positive individuals and supported by the number of hip surgeries done in the HIV positive cohort (21%) who were below the age of 50 years compared to 5% in the HIV negative group who had hip surgery and were above the age of 50 years. Despite being of younger age when having hip surgery, this patients still had high D-dimer values after surgery. This contrary to studies have shown that there dramatically increased risk of venous thrombosis associated with age, there are also increases in markers of intravascular coagulation such as D-dimer and prothrombin fragments indicating that there is a persistent hypercoagulable state [16]. In the study by Nkhoma et al which looked at the level of D-dimer values in HIV positive ART naïve patients, it was observed that D-dimers measured prior ART initiation were significantly raised compared to HIV negative controls [31]. Viral replication or persistence, high levels of bacterial lipopolysaccharides (LPS), bacterial DNA and their associated immune activation

as well as higher levels of bioactive Tissue Factor (TF) the major in vivo activator of coagulation in HIV positive individuals than do samples from HIV negative controls may explain the high D-dimer levels [32]. This may explain why younger HIV positive orthopedic patients having a hip replacement surgery, tended to have as high D-dimer compared to HIV negative individuals undergoing a similar procedure.

After surgery strict anti-deep vein thrombosis measures, and pharmacologic prophylaxis (when available or affordable by the patient) are employed in the prevention of DVT. Despite not receiving post-operative pharmacoprophylaxis and having high positive post-operative positive D-dimers values, only one in each cohort developed symptomatic DVT as predicted by the incidence of 4% proposed by Falck-Ytter et al [12]. Mechanical prophylaxis, which include graduated compression stockings alone can half the rates of DVT [34]. Ninety-five percent of all the study patients received early mobilization in form of active or passive physiotherapy. This may be the may be the reason why they did not go on to develop clinical DVT despite having high D-dimer values. Our robust early mobilization post-operative policy which is implemented with the help of qualified physiotherapy team is an invaluable asset in both prevention of post-operative morbidity like DVT and PE as well as improving functional outcomes of our patients. Therefore the lower prevalence of DVT after major orthopedic surgery than expected is an indication of good practices in the prevention of DVT at the University of Teaching Hospital, Lusaka.

This study did not look into the prevalence of asymptomatic DVT in these patients, which is DVT with positive ultrasound or venography result but no clinical signs and was reported to be as high as 9.4 % in the study done by Mundama et al in the medical patients. Although the incidence of asymptomatic DVT is greater than that of symptomatic DVT, the clinical importance of asymptomatic DVT remains unclear [33]. Thus there may be a need to further study the prevalence of asymptomatic DVT in our surgical patients which may also be high give the high D-dimer values found in this study. The high morbidity and mortality rate in patients with asymptomatic proximal DVT underscores its clinical relevance and supports

targeting of asymptomatic proximal DVT as an appropriate endpoint in clinical trials of thrombo-prophylaxis [34].

After undergoing major orthopedic surgical procedure only 4.3 % (n=2) were negative for D-dimers (true negatives). The HIV negative individual was in the 31-40 age group and underwent spinal surgery while the other was HIV positive in 41-50 age group after ankle surgery. Both were female. The HIV positive patient had a CD4 count above 500 cells/ul and had been on a Truvada and Nevirapine based regimen for more than 3 years. It difficult to draw statistically relevant conclusions from this result because of the small number that were D-dimer negative but of note is that they was equal distribution in the cohort and control group.

CHAPTER SIX: CONCLUSION

6.1 Conclusion

The study showed that:

1. HIV is not an added risk to major orthopedic surgery patients developing DVT. There was no difference in the prevalence of DVT in HIV positive and HIV negative patients following lower limb and spinal surgery at the University Teaching Hospital in Lusaka.
2. Major orthopedic surgery is a risk in the development of DVT as shown by the high D-dimer levels in both cohorts: 94.7% in HIV positive and 95.7% in HIV Negative individuals
3. The study showed that the lower prevalence of symptomatic DVT (5.3%) is due to careful patient selection and routine use of non-pharmacological anti –DVT measures
4. The prevalence of acute symptomatic clinical DVT, confirmed by ultrasonography is both cohorts HIV Positive and HIV negative was 5.3% and 4.7 % respectively. The prevalence of DVT could have been higher if non-symptomatic DVT was considered in view of high D-dimer values in both cohorts.

Thus was no difference in the prevalence of DVT in HIV positive and HIV negative patients following lower limb surgery and spinal surgery at the University Teaching Hospital in Lusaka.

6.2 Recommendations

1. Further studies on the prevalence of DVT in HIV orthopaedic patients should include asymptomatic DVT
2. Protocols should be developed to be used in the management of major orthopaedic surgery. The protocols should include routine use of D-dimers value and HIV testing
3. Further studies should be done to assess sensitivity and specificity and predictive value of d-dimers in the development of DVT in our population.

6.3 Study Limitations

1. The two cohorts were not matched for age, sex and type of surgery in the sampling process. This would have made comparisons between the two groups more accurate.

2. The study did not score the patients for risk of DVT prior to selection although the exclusion criteria effective ruled out high risk patients from being selected.
3. The study did not look for asymptomatic DVT in the patients as there is no agreed upon protocol for the treatment of this type of DVT at the hospital. Patients at high risk are given prophylaxis if available, while those with clinical confirmed DVT are treated on anticoagulant therapy. There is no set protocol as to whether asymptomatic DVT should be give just prophylaxis or treated with anticoagulant therapy since most asymptomatic DVT resolves spontaneously

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APPENDICES

Appendix 1

Patient Data Sheet:

1. **Patient Study ID Number:_____**
2. **Hospital ID:_____**
3. **Demographics:**

3.1. What is your age?

21-30 (0) 31-40 (1) 41-50 (2) 51-60 (3) 61-70 (4) >71 (5)

3.2. What is your sex?

Male (0) Female (1)

3.3. What is your ethnicity?

African (0) Asian (1) Caucasian (2) Mixed (3)

4. **What has been your HIV status in last 3 months?**

Positive (0) Negative (1)

4.1. If Positive what is your CD4 count in the last 3 months?

0-200(0) 201-500(1) >500 (2) Not Available (3)

5. **Are you on Anti-Retroviral Therapy?**

Yes (0) No (1)

5.1. If yes which combination?

_____

5.2. How long have you been on this combination?

< 6 months (0) 6-12 months (1) 1 year – 3 years (2) more than 3 years (3)

5.3. Do you Smoke?

Yes (0) No (1)

6. **Type of surgery are you planned for?**

Elective (0) Emergency (1)

Post-Operative Patient Data:

1. **Patient Study ID Number**:_____
2. **Patient Hospital ID**:_____
3. **Type of Surgery was done?**

Hip Surgery (0) Knee Surgery (1) Femur Surgery (2)

Tibia/ Fibula Surgery (3) Ankle Surgery (4) Pelvic Bone Surgery (5)

Spinal Surgery (6)

4. **What was duration of surgery?**

< 30hr (0) 30min to 1hr (1) 1hr -2hrs (2) 2hrs -3hrs (3)
more than 3 hrs (4)

5. **Was Deep Vein Thrombosis drug prophylaxis given?**

Yes (0) No (1)

6. **Where Deep Vein Thrombosis compressive stockings after surgery used?**

Yes (0) No (1)

7. **Was post-operative physiotherapy (early mobilisation) started?**

Yes (0) No (1)

8. **D-Dimer Test :**

8.1. On which post-operative day was the sample taken?

3 (0) 4 (1) 5 (2)

8.2. What was the result?

Positive (0) Negative (1)

9. Did the patient develop any clinical signs of DVT:

Pitting oedema (0) Tenderness (1) Erythema (2) Warm to touch (3) No Signs (4)

10. If the patient developed clinical signs of DVT was a Doppler Venous Sonography done to confirm?

10.1. Yes (0) No (1)

10.2. If Yes on which post-operative day was it done?

4 (0) 5 (1) 6 (2) 7 (3) 8 (4) 9 (5) 10 (6)

10.3. What was the result?

Positive (0) Negative (1)

10.4. If positive what was the site of thrombosis?

Tibia (0) Popliteal (1) Femoral (2) Iliac (3)

Appendix 2

D-dimer reference range **0-500 ng/dl (0-0.5 ug/dl)** as normal range

The D-dimer were tested using the *VIDAS© D-Dimer Exclusion II®* which is an automated quantitative test for immune-enzymatic determination of fibrin degradation products in human plasma stored in sodium citrate using enzyme linked fluorescent assay with measurement range of 45ng/ml to 10000 ng/ml

Use:

The D-dimer assay can be used to rule out deep vein thrombosis (DVT) and pulmonary embolism.

Limitation:

Elevated D-dimer levels occur in a number of clinical situations and are not diagnostic of any specific condition. Results for patients undergoing anticoagulant therapy should be interpreted with caution because D-dimer levels do not tend to increase to the same degree as in patients not receiving anticoagulants. Levels can be increased in individuals with cancer, underlying inflammation, atherosclerotic vascular disease, pregnancy, and in liver disease due to decreased hepatic clearance. Levels increase with age.

4 mls of venous blood sample collected in a light blue top bottle **(Sodium Citrate)** and analysed within 1 hour of collection transported under ice for D-dimer test.