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Descriptive study of Venous Thromboembolic Disease in the adult population admitted to Tshepong Hospital comparing the proportion of HIV and non-HIV infected patients

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A research report submitted to the University of Witwatersrand, Johannesburg in fulfilment for the requirements of the degree of Master of Medicine
4 June 2019

DECLARATION

I, Pramodhini Moodley, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……..
Pramodhini Moodley
Signed ……. day of ……2019

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PRESENTATIONS ARISING FROM THIS PROJECT

1) November 2016: SoMCHAT (Soweto Matlosana SAMRC Collaborating Centre for HIV/AIDS and TB) Mini Conference – Oral presentation

2) September 2016 : Wits Research Day and Post Graduate Expo – Poster presentation

ABSTRACT

Background

HIV and TB independently incur increased risk for venous thromboembolic disease (VTE): deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Data from high HIV and TB burden settings describing VTE is scarce. The Wells' DVT and PE scores are widely used but their utility in these settings has not been reported on extensively. We therefore report clinical and treatment aspects of in-patients with newly diagnosed VTE to assess HIV and TB prevalence, and their Wells' score.

Setting

Tshepong Hospital in the North West Province of South Africa.

Methods

A prospective cohort of adult in-patients with radiologically confirmed VTE were recruited. Demographics, presence of TB, HIV status, duration of treatment, CD4 count, viral load, VTE risk factors, and parameters to calculate the Wells' score were collected.

Results

One hundred patients were recruited, of whom 59 were HIV-infected; 39 had TB disease and 32 were HIV/TB co-infected. Eighty -three patients had a DVT only; 11 patients had a PE, and six had both a DVT and PE. Eighteen of 42 patients on antiretroviral treatment (ART) were on treatment for less than six months. Twenty patients of 39 were on TB treatment for less than one month. The median DVT and PE Wells' score in all sub-groups was 3.0 (IQR: 1.0-4.0) and 3.0 (IQR: 2.5-4.5), respectively. There were nine deaths.

Conclusion

HIV /TB co-infection appear to confer a risk for VTE, especially early after ART and/or TB treatment, and therefore require careful monitoring for VTE and early initiation of thrombo-prophylaxis.

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ABBREVIATIONS

ACA: Anti-cardiolipin antibody
ART: anti-retroviral treatment
BMI: body mass index
CD154: cluster of differentiation 154
CD4: cluster of differentiation 4
CD40L: cluster of differentiation 40 ligand
CD8: cluster of differentiation 8
CTPA: Computed tomography pulmonary angiogram
DVT: deep vein thrombosis
ECG: electrocardiogram
FDC: fixed dose combination
ICAM-1: intercellular adhesion molecule 1
LA: lupus anticoagulant
PAI-1: plasminogen activator inhibitor 1
PE: pulmonary embolism
HIV: human immunodefiency virus
TB: tuberculosis
VCAM-1: vascular cell adhesion molecule 1
VTE: venous thromboembolism
WHO: World Health Organisation
IRIS: immune reconstitution inflammatory syndrome

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 INTRODUCTION

1.1.1 Venous thromboembolic disease

Venous thromboembolic disease (VTE) is the abnormal formation of clots in the venous system. VTE most commonly presents as deep vein thrombosis of the (lower extremity most commonly) and pulmonary embolus.

Annual incidence of VTE is approximately 100/100,000 per annum in the US[1] .Two hundred thousand South Africans are estimated to present with deep vein thrombosis(DVT) each year[2] .Venous thromboembolism is associated with significant morbidity and mortality involving cardiac and pulmonary complications such as hypoxaemia, increased pulmonary vascular resistance (pulmonary hypertension) leading to right heart failure, post phlebitic syndrome and bleeding, the latter an effect of anticoagulant therapy[3].It is therefore important to identify those at high risk who may benefit from early prophylaxis and treatment[4].

1.1.2 Impact of HIV/AIDS and Tuberculosis

Seven million South Africans (12.7%) are Human Immunodeficiency Virus (HIV) infected, of whom almost four million are receiving antiretroviral therapy (ART) [5]. The World Health Organisation (WHO) reports that annual incidence of tuberculosis (TB) in South Africa in 2017 to be 567/100,000 [6].In South Africa over 60% of TB patients are co-infected with HIV[6] and most will receive ART with TB treatment at some stage during their treatment for TB[7,8]

1.1.3 HIV and VTE

The relationship between HIV and the risk for VTE has been established[9]. Numerous studies suggest a two to tenfold increased risk of VTE in HIV positive patients compared to non HIV infected individuals [3,4] .The frequency of VTE in the HIV population has been reported to range between 0.19% - 7.63%[4] .HIV has been identified as a prothrombotic condition. Classically Virchow's triad (hypercoagulability , endothelial dysfunction , stasis) has been used to describe the risk of thrombosis[10].It is postulated that HIV may lead to a hypercoagulable state due to , amongst other factors, protein S deficiency, protein C deficiency, anti-thrombin

deficiency[4] , increased expression of tissue factor on monocytes , higher D- dimer values , mild to moderate hyperhomocystinaemia, higher levels of anticardiolipin antibodies and lupus anticoagulant as well as endothelial dysfunction leading to increased expression of von Willebrand factor[11] , plasminogen activator inhibitor-1 and factor V (Figure1).

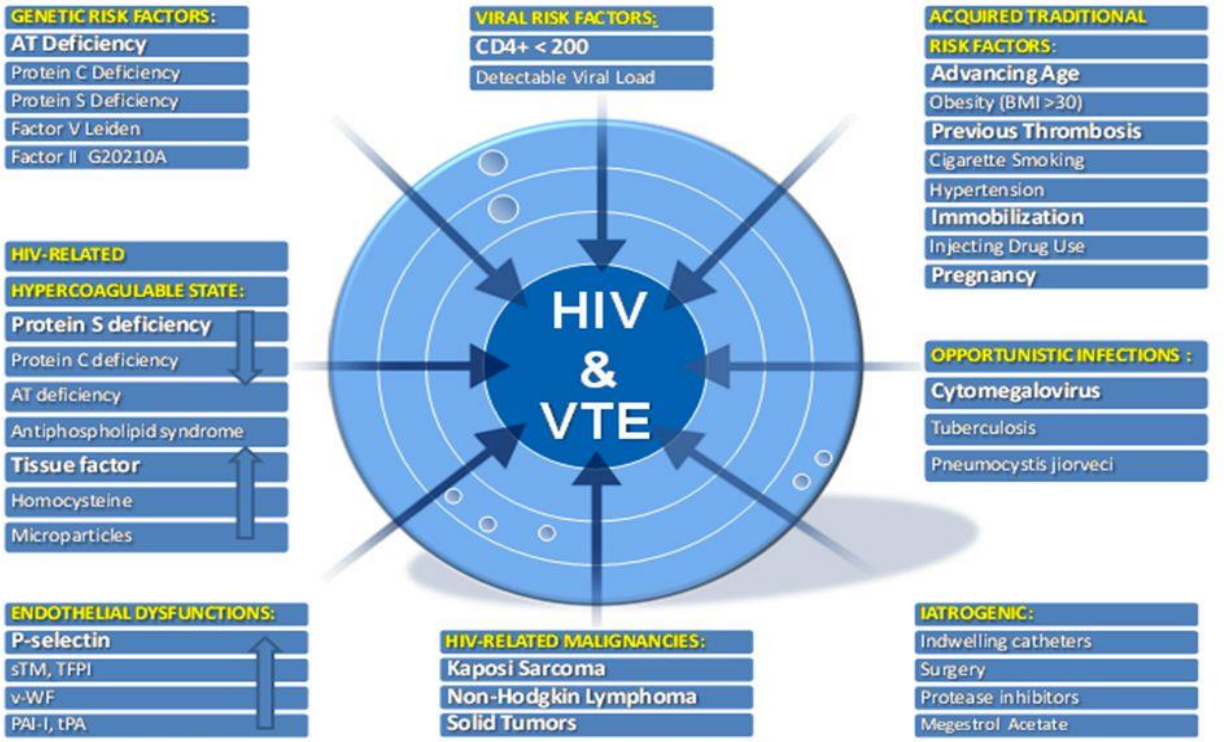


Figure 1: Multi-factorial etiology of HIV-related venous thromboembolism. AT, antithrombin; sTM, soluble thrombomodulin; TFPI, tissue factor pathway inhibitor; v-WF, von Willebrand Factor; PAI-I, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator. Stronger risk factors for VTE are listed in bold.

Figure 1: Multifactorial aetiology of HIV related venous thromboembolism[4]

Protein S levels (free levels in serum) are found to be lower in chronic inflammatory states such as HIV, due to an elevation in C4b-binding protein which binds to Protein S [12].Heightened activation of T cells with micro particle release may be a contributor due to the binding of micro particles to Protein S which decreases free Protein S. Decreased protein synthesis and anti-protein S antibodies have also been noted in HIV population group[11]. Hyperhomocystinaemia is commonly seen in 11-29% HIV positive patients[4] which poses an additional prothrombotic risk. The mechanisms involved may include increased reaction of platelets, disruption of fibrinolysis and increased activity of adhesion molecules, cytokines and tissue factor.

Antithrombin deficiencies are due to decreased liver synthesis, increased renal losses and direct inactivation[13].Anticardiolipin antibodies (ACA) and lupus

anticoagulant (LA) form part of the antiphospholipid syndrome, known to be associated with increased risk of thrombosis. ACA as well as LA have been found in varying rates in HIV positive individuals; however there is no clear, strong association between positive ACA, LA and VTE occurrence. The alteration toward a hypercoagulable state may add additional risk of VTE but may not be solely responsible for VTE episodes[14].

Endothelial dysfunction and activation has shown significant relation to VTE. Under normal circumstances the endothelium provides a vasodilatory and antiplatelet function. Activation of the endothelial cell may lead to expression of procoagulant proteins and haemostatic dysfunction[11] .In a prospective study, 306 Kenyan women were followed after acquiring HIV-1 infection with biomarkers for endothelial activation, namely soluble vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1(ICAM-1) being measured during the pre-infection, acute and chronic infection stages. Results reviewed showed a global increase in biomarkers during all stages of infection[15]. In a study of 32 HIV untreated patients, it was found that higher Interleukin 6 (IL-6) and D-dimer levels were linked to vascular dysfunction as evidenced by higher endothelial biomarker levels specifically E Selectin and ICAM-1.Changes in the endothelial cell surface by numerous pathogens can cause the endothelial surface to become more prothrombotic. Activation of endothelial cells leads to increased tissue factor mediated thrombin generation, alteration in anti-coagulant pathways and depressed fibrinolysis[13].During inflammation antithrombin III, tissue factor pathway inhibitor and plasminogen activator inhibitor are important in producing a hypercoagulable state[13]. Endothelial dysfunction may also lead to increased expression of von Willebrand factor[11], and factor V which play a role in clot formation[4]. The immune mediator CD40 and associated CD40 ligand (CD40L or CD154) have now been shown to play a role thrombosis. The presence of CD40 has been noted in monocytes, macrophages, smooth muscle cells, and endothelial cells. If CD40 is activated, the above cells state releasing adhesion receptors, pro-inflammatory cytokines, tissue factor, metalloproteinases and prostaglandins. If platelets are stimulated by CD40 the inflammatory cascade may be heightened with leukocytes also being recruited to sites of thrombus formation. Levels of CD40L are noted to be higher in HIV positive patients[16]. The cellular remains or remnants of platelets, lymphocytes, and

endothelial cells are known as micro particles[4]. Micro particles are found in higher levels in HIV positive patients (due to release of CD4 micro particles causing cell apoptosis) and are thought to collect coagulant factors upon their surfaces[4].

Studies done assessing the risk of VTE in HIV patients with varying degrees of immunosuppression have suggested that a lower CD4 count may predispose to an increase risk of VTE[3, 5, 14]. A retrospective study of 131 HIV infected patients showed a 30-fold increase rate in thrombotic events in patients with a CD4 count <200cells/mm[17]. It has been suggested that a lower CD4 count may be related to a progressively more hypercoagulable state[42]. This may be explained by Protein C and S deficiency commonly found in patients with more developed immunosuppression. While most cases may occur at a lower CD4 count, thrombotic events have been noted to occur over a wide range of CD4 counts[14, 18]. A higher viral load may also be associated with a hypercoagulable state. A state of advanced immunosuppression (as evidenced by a low CD4 count and higher viral load) may induce immune and inflammatory activation resulting in increased coagulability and thereby VTE occurence[14].In a retrospective study carried out in San Diego, California it was noted that most patients with HIV and concurrent VTE present at a younger age compared to the general population upon a retrospective study [14].The mean age has however increased in the post HAART era[14.]

It has been suggested by certain studies that protease inhibitors may increase risk of VTE[42] due to disruption of hepatic metabolism via the cytochrome P450 system associated with regulation of thrombotic proteins, dysregulation of the anticoagulant nature of the body and possible endothelial and platelet dysfunction. In a study by Koppel et al, levels of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) were higher in patients on antiretroviral regimens containing protease inhibitors. There have also been reports of increased coronary artery disease, insulin resistance, diabetes as well as peripheral vascular disease[20] due to hypercholesterolemia. Higher plasma lipid levels as well as the lipodystrophy syndrome, which are associated with protease containing ART, may also contribute to a hypercoagulable state with decreased fibrinolysis[13, 21]. The protease inhibitor most frequently associated is Idinavir[14]. There have however been studies showing no specific risk for acquiring VTE[4, 14].

1.1.4 VTE and TB

Opportunistic infections such as tuberculosis, cytomegalovirus and pneumocystis pneumonia have been shown to add additional risk[4] due to the augmentation of risk for VTE .This is either due to the infection itself or the related treatment. In patients with TB there is a demonstrated higher incidence of VTE [22], largely due to a hypercoagulable state. This has been demonstrated in a cross-sectional study carried out in which 47 percent of new DVT cases amongst HIV patients admitted had concomitant TB[13].There is however less data describing possible aetiological mechanisms between TB and VTE. TB may be viewed as an independent risk factor for VTE. In a study involving patients with active TB[23], it was shown that study participants had increased fibrinogen, Factor VIII and Plasminogen activator I plasma levels (linked to low antithrombin III and low protein C). This evidence was supported by a prospective study which[24] demonstrated elevated plasma fibrinogen, impaired fibrinolysis and decreased antithrombin III levels in patients with active TB. The use of rifampicin has also been shown to increase the risk of developing a DVT probably, due to alteration in anticoagulant protein production within the liver[25].

Most VTE episodes appear to involving deep vein thromboses followed by pulmonary emboli as demonstrated by a case review of 30 HIV positive patients in Boston, Massachusetts[19].

1.1.5 Drug interactions

In high HIV and TB burden settings, VTE therapy is complicated by drug-drug interactions between coumadin-based treatments for VTE. Warfarin co-administered with rifampicin[26, 27, 28], non-nucleoside reverse transcriptase inhibitors and protease inhibitors[29] make monitoring and management of patients with VTE complex for both the patient and the clinical service. Newer anticoagulants like dabigatran and rivaroxaban have not been evaluated in patients receiving therapy for TB or HIV [29, 30]. These agents have however been shown to be as effective and also cost effective in high income countries[31].

1.1.6 Traditional Risk factors

Traditional, well documented risk factors for VTE include, amongst others: older age, obesity[32] (namely increased adiposity) [33], smoking[32], immobilization longer than three

days; pregnancy and the postpartum period[34]; major surgery in previous four weeks; long plane or car trips (> four hours) in previous four weeks[35]; cancer, previous DVT, lower extremity fractures, antithrombin III, protein C deficiency, protein S deficiency, factor V Leiden and hormone replacement therapy.

1.1.7 Pre-test probability- Well's criteria

Well's criteria for the clinical assessment of pulmonary embolism[36] (Table 1) and Well's criteria for the probability of DVT[37] (Table 2) are commonly used to assess the probability of pulmonary embolism and deep vein thrombosis respectively[38].

The presence of specific clinical parameters contribute to a composite score; low scores imply a low probability[38] and high scores an increased probability for VTE, and suggest further investigation is required. Few studies have reported Wells' score in patients from sub-Saharan Africa. Evidence or history of either HIV-infection or TB disease is not part of the Wells' scoring system.

Table 1: Wells criteria and modified Wells criteria: clinical assessment for pulmonary embolism[36]

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1.0
Malignancy	1.0
Probability	**Score**
Traditional clinical probability assessment (Wells criteria)	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment (Modified Wells criteria)	
PE likely	>4.0
PE unlikely	≤4.0

Table 2: Pre-test probability of deep vein thrombosis (Wells score) [37]

Clinical feature	Score
Active cancer (treatment ongoing or within the previous six months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (no varicose)	1
Alternative diagnosis as likely or more likely than that of deep venous thrombosis	-2
Score	
High probability	3 or greater
Moderate probability	1 or 2
Low probability	0 or less
Modification:	
This clinical model has been modified to take one other clinical feature into account: a previously documented deep vein thrombosis (DVT) is given the score of 1. Using this modified scoring system, DVT is either likely or unlikely, as follows:	
DVT likely	2 or greater
DVT unlikely	1 or less

1.1.8 Justification for the study

Both HIV infection and TB confer an increased risk for VTE. However; there is a paucity of published data describing VTE in HIV/TB co infection. Anecdotally, in

hospital practice, there is significant group of HIV/TB co-infected patients who present to hospitals with VTE. This study aims to determine the proportion of patients with confirmed, new episode of venous thromboembolic disease who are HIV positive, have TB or are HIV/TB co-infected.

1.2 OBJECTIVES

1.2.1 PRIMARY OBJECTIVE

To determine the proportion of newly diagnosed adult patients with venous thromboembolic disease at Tshepong Hospital who are HIV positive, who are diagnosed as having TB, or who are HIV and TB co-infected.

1.2.2 SECONDARY OBJECTIVES

1. To report proportion of patients with confirmed venous thromboembolic disease with particular regard to:
    a. HIV
        i. HIV status, Antiretroviral (ART) status, treatment – onset, ART duration and regimen, immunological and virological response
    b. TB Infection,
        i. TB status, TB treatment – onset, duration, regimen, site of TB
    c. Traditional risk factors for venous thromboembolic disease, not included as part of Well's scoring system: pregnancy and post-partum state; oral or injectable contraception use within the last three months; obesity, smoking, recent long distance travel
    d. Classify patients with HIV, TB and HIV-TB co-infection according to the Well's scoring criteria for DVT and PE, and look at the proportions of individuals within each pre-test probability group.

1.3 METHODOLOGY

1.3.1 STUDY DESIGN

A prospective study looking at adult patients of Tshepong Hospital presenting with venous thromboembolism, with a view to assessing the proportion of patients with HIV, TB and HIV/TB co-infection.

1.3.2. STUDY POPULATION AND SAMPLE

LOCATION

Tshepong Hospital (single centre study)

POPULATION

Adult patients treated at Tshepong Hospital with a new diagnosis of venous thromboembolic disease.

INCLUSION CRITERIA

1. Age older than 18 years
2. Venous thromboembolism in the form of deep vein thrombosis (confirmed by positive findings on Doppler ultrasound of the extremity showing a non-compressible vein, thrombus, or flow disturbance) or pulmonary embolism seen on Computed tomography pulmonary angiogram (CTPA) as filling defects within the pulmonary arteries. Cases with positive findings will be identified by the Radiology team, and recorded on reports which are filled in duplicate. Radiology records will be reviewed daily in consultation with the radiology team in order to identify patients.

EXCLUSION CRITERIA

1. Past history of proven thromboembolic disease on anticoagulation.
2. Patients unable to provide written consent.
3. Patients with insufficient data (transferred, discharged or demised)
4. Patients refusing to be tested for HIV.
5. Patients refusing access to medical and laboratory records (including CD4 and viral load)

SAMPLE SIZE AND DURATION

All eligible patients will be invited to participate in the study. Upon review of radiology records and consultation with the Radiologists, it is currently estimated that five patients per week meet the inclusion criteria and are diagnosed with a deep vein thrombosis by the ultra sonographer, with two diagnoses of pulmonary embolism per week on CTPA. One hundred patients will be recruited for the study. It is predicted

that approximately two thirds of these patients will be HIV positive i.e. sixty-seven patients being reviewed with VTE and associated HIV infection.

1.3.3 STATISTICS AND ANALYSIS

The patient names will not be entered in the data collection sheets instead codes will be used- all results will be reported in aggregate. Data will be collected for each patient and compared within various sub-categories e.g. patients with HIV infection compared to non-HIV infection. The proportion of patients that fit into the different pretest probability groups (high, moderate, low) will be calculated. Multivariate analysis will be used to compare different risk factors. Comparisons of continuous variables between patients groups will be done by *t*-test (parametric) or Wilcoxon rank sum test (non-parametric).Categorical variables will be compared using Fisher's exact test. The correlation coefficient will be used to compare continuous variables to one another. The statistical significance will be calculated at the 95% confidence level.

1.3.4. METHODS AND TECHNIQUES

A data sheet will be used to record all information during patient interview, examination and record review

RECRUITMENT

The radiology team will be consulted each day in order to review the records of confirmed cases of deep vein thrombosis and pulmonary embolism. Patients will then be approached and invited to participate.

PATIENT INTERVIEW

Written informed consent for participation in the study will obtained. All consenting participants will be questioned regarding their demographics:

1. Age
2. Gender
3. Ethnicity
4. HIV serostatus
    a. If HIV positive, date of diagnosis
    b. Details of compliance with ARV

c. If patient's HIV status is unknown or they have tested negative within the last month, they will be followed up within their admission stay in hospital to document the results of voluntary counselling (offered as per routine hospital practice- Annexure A).

5. An enquiry about TB as a comorbidity (diagnosis and treatment).

Risk factors

6. Current history of active malignancy: whether active cancer (currently being treated for malignancy, having received treatment within last six months, or undergoing palliative care) [36, 37], site of the malignancy.
7. Immobility and functional capacity will be assessed according to the Karnofsky score[39](see Annexure B), as well as duration of immobility (within last 3 days)
8. Major Surgery including all surgery lasting more than 45 minutes (this may include spinal surgery, neurosurgery, abdominal, pelvic), all intra-abdominal surgery, all extensive bone and joint surgery occurring within the last four weeks[37, 38].
9. History of long distance travelling lasting more than six hours in the last four weeks
10. For female participants
    a. Contraceptive use (oral, injectable, implants) in the last 3 months[40, 41]
    b. Currently pregnant or post-partum (up to 28 days)[34]
11. Tobacco history: number of cigarettes (including pipes and roll up cigarettes) per day and the duration of years smoking

Further History

12. Current History of paralysis or paraplegia
13. Current History of lower limb in a cast.

Symptom History

14. Patients will be questioned regarding the onset of symptoms of deep vein thrombosis namely: swelling of entire affected leg/s, localized tenderness[37] as well as pulmonary embolism i.e. sudden shortness of breath, sudden chest

pain, dizziness and /or collapse or haemoptysis in relation to diagnostic tests being done.

INVESTIGATIONS

Laboratory

1. No additional research samples will be taken and no investigations requested outside standard practice of care.

Non invasive

2. The ECG[42] of patients with pulmonary embolism will be reviewed. It will be noted as to whether the following changes are seen:
    i. Sinus tachycardia (heart rate > 100 beats per min.)
    ii. Complete Right bundle branch block
    iii. Right ventricular strain pattern
    iv. Right axis deviation
    v. Dominant R wave in V_1
    vi. Peaked p waves in lead II (p pulmonale)
    vii. $S_I Q_{III} T_{III}$ change
    viii. Non-specific T wave changes

Radiology

3. The chest X-ray will be reviewed in patients diagnosed with pulmonary tuberculosis and the findings with regard to normal features, cavitation, miliary pattern, infiltrates (unilateral or bilateral) recorded. The area of lung affected (divided into six zones) as well as zonal changes will be noted.

EXAMINATION

1. Patients will be examined for swelling of the entire affected leg, as well as associated tenderness with or without pitting oedema.
2. Calf swelling of more than three cm of the affected leg will be assessed by measuring the circumference of the calf 10cm below the tibial tuberosity. The skin of the affected leg will be inspected for any collateral non varicose superficial veins[37].

3. Patients weight and height will be measured

PATIENT RECORDS

1. Patient's medical records (admission notes, clinic notes) will be reviewed to obtain any information that was unclear on interview.
2. Information regarding the current TB drug regimen and HIV drug regimen.
3. If the patient is HIV positive and on ART, the latest CD4, viral load, cardiac enzymes (in the case of pulmonary embolism, if available) and D-dimer levels (in the case of deep vein thrombosis, if available) will be abstracted.
4. If the patient is newly diagnosed HIV positive, a CD4 will be abstracted (the CD4 count is done routinely in keeping with National Guidelines)
5. For those who have been diagnosed with TB, the site of TB (pulmonary, abdominal, TB meningitis, bone marrow, lymph nodes) and the mode of diagnosis will be noted for pulmonary TB (Gene Xpert, Line probe assay, empiric)

1.4 ETHICS

Ethical approval will be obtained by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg.

Consent will be obtained from the Head of the Department of Internal Medicine as well as the CEO of Klerksdorp/Tshepong Hospital Complex. Each patient will be consented individually. Individual numbers will be assigned to each patient sequentially. Confidentiality will be ensured with subject identifiers rather than personal names. Limited access to data (Principal researcher, supervisors) will further ensure confidentiality.

1.5 FUNDING

Research costs will include stationery, photocopying, printing of data and travelling which will amount to approximately ZAR 5,000. PHRU Research funds will cover costs to a value of ZAR 40,000. These funds may be utilized to employ a study nurse to assist with collection of data, and interpretation (patient interview).

1.6 LIMITATIONS

Prospective studies are always subject to disease patterns and variable patient numbers. The study is based in a referral hospital which may influence numbers upwards and not be representative of a local community. Patients presenting with earlier symptoms may not be referred by the clinic until a later stage. Those who are too ill may be unable to consent.

1.7 TIME SCHEDULE

Task	**Time Required**	**Deadline**
Submit application for ethical clearance		31 July 2015
Submission for assessor group meeting		21 August 2015
Present protocol to assessor group	30 minutes	8 September 2015
Refine protocol , data capture sheet and analysis model with supervisor	± 2 hours	July 2015
Study preparation • Finalise tools • Data collection • Data analysis and results	±6 months	July 2015- December 2015
Submit data analysis and results write-up to supervisor and an outline of what will be included in research article		Mid-February 2016
Supervisor feedback	±3 hours	End February 2016
Research article writing	3-4 weeks	End March 2016
Submit first draft of research article to supervisor		End March 2016
Prepare article for submission	3-4 weeks	End May 2016
Submit research article for examination		June 2016
Disseminate article on approval		September to October 2016

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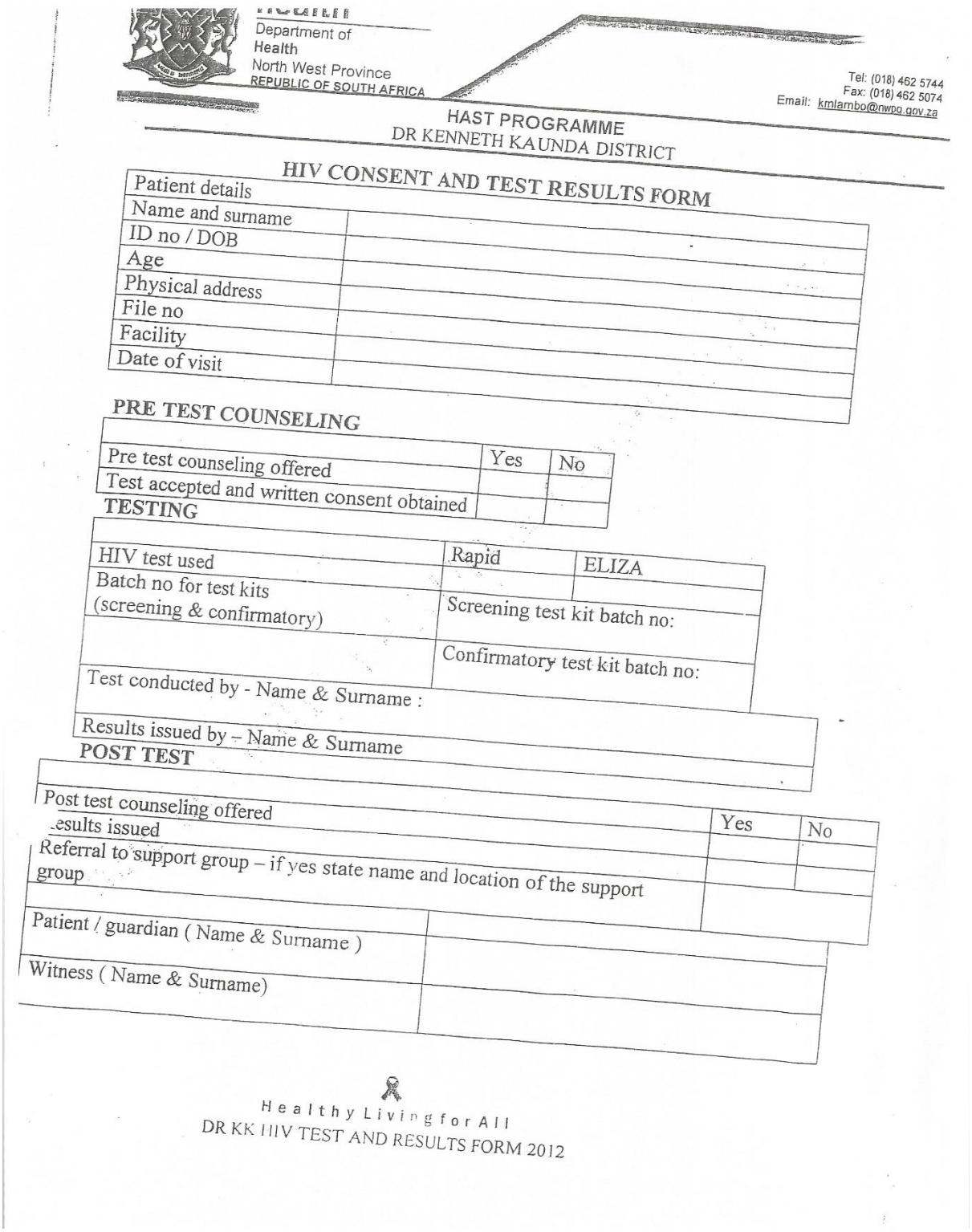
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1.9 ANNEXURES

Annexure A



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HAST PROGRAMME
DR KENNETH KAUNDA DISTRICT

HIV CONSENT AND TEST RESULTS FORM

Patient details	
Name and surname	
ID no / DOB	
Age	
Physical address	
File no	
Facility	
Date of visit	

PRE TEST COUNSELING

	Yes	No
Pre test counseling offered		
Test accepted and written consent obtained		

TESTING

HIV test used	Rapid	ELIZA
Batch no for test kits (screening & confirmatory)	Screening test kit batch no:	
	Confirmatory test kit batch no:	
Test conducted by - Name & Surname :		
Results issued by – Name & Surname		

POST TEST

	Yes	No
Post test counseling offered		
Results issued		
Referral to support group – if yes state name and location of the support group		
Patient / guardian (Name & Surname)		
Witness (Name & Surname)		

Healthy Living for All
DR KK HIV TEST AND RESULTS FORM 2012

Annexure B

KPS score	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary: active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

KPS = Karnofsky Performance Score.

CHAPTER 2: SUBMISSIBLE ARTICLE

TITLE PAGE

a) Descriptive study of Venous Thromboembolic Disease in the adult population admitted to Tshepong Hospital comparing the proportion of HIV and non-HIV infected patients

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09/2016: Research Day and Post Graduate Expo, University of the Witwatersrand, Johannesburg, South Africa

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Soweto Matlosana Collaborating Centre for HIV/AIDS and TB, University of the Witwatersrand, Johannesburg, South Africa
Tshepong Hospital, Matlosana, North West Provincial Department of Health.

g) Running head: HIV AND NON-HIV WITH VENOUS THROMBOEMBOLISM

Abstract

Background

HIV and TB independently incur increased risk for venous thromboembolic disease (VTE): deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Data from high HIV and TB burden settings describing VTE is scarce. The Wells' DVT and PE scores are widely used but their utility in these settings has not been reported on extensively. We therefore report clinical and treatment aspects of in-patients with newly diagnosed VTE to assess HIV and TB prevalence, and their Wells' score.

Setting

Tshepong Hospital in the North West Province of South Africa.

Methods

A prospective cohort of adult in-patients with radiologically confirmed VTE were recruited. Demographics, presence of TB, HIV status, duration of treatment, CD4 count, viral load, VTE risk factors, and parameters to calculate the Wells' score were collected.

Results

One hundred patients were recruited, of whom 59 were HIV-infected; 39 had TB disease and 32 were HIV/TB co-infected. Eighty -three patients had a DVT only; 11 patients had a PE, and six had both a DVT and PE. Eighteen of 42 patients on antiretroviral treatment (ART) were on treatment for less than six months. Twenty patients of 39 were on TB treatment for less than one month. The median DVT and PE Wells' score in all sub-groups was 3.0 (IQR: 1.0-4.0) and 3.0 (IQR: 2.5-4.5), respectively. There were nine deaths.

Conclusion

HIV /TB co-infection appears to confer a risk for VTE, especially early after ART and/or TB treatment, and therefore require careful monitoring for VTE and early initiation of thrombo-prophylaxis.

Key words: deep vein thrombosis, pulmonary embolism, venous thromboembolism, prevalence, tuberculosis, HIV

Introduction

Venous thromboembolic disease (VTE) in the form of deep vein thrombosis (DVT) and pulmonary embolism (PE), is estimated to affect 1/10,000 people in the United States annually[1], and 200,000 South Africans are estimated to present with DVTs each year [2]. Venous thromboembolism is associated with significant morbidity and mortality, added to by long term anticoagulation therapy for treatment and prevention of recurrence.

Human immunodeficiency virus is a clear risk factor for VTE disease with studies suggesting up to a tenfold increased risk of developing VTE [2, 3]. In HIV-infected individuals, protein C, and S deficiencies, raised circulating pro- inflammatory markers [3-5], and endothelial dysfunction [3, 4, 6-9] are apparent risk factors for VTE. Furthermore treatment with protease inhibitors, immune reconstitution inflammatory syndrome (IRIS) and comorbid opportunistic infections are additional risk factors [4, 10, 11, 12]. Patients on antiretroviral treatment (ART) live longer, increasing the pool of individuals at risk for VTE [10]. Seven million South Africans (12.7%) are HIV-infected, of whom almost four million are receiving antiretroviral therapy (ART) [13].

The World Health Organisation (WHO) reported the annual incidence of tuberculosis (TB) in South Africa in 2017 was 567/100,000 population [14]. Tuberculosis is also a clear risk factor for VTE. Increased fibrinogen, factor VIII, plasminogen activator I and decreased anti-thrombin contribute to this risk[15]. Severe TB is linked to disrupted fibrinolysis, decreased anti-thrombin III and thrombocytosis which promote a hypercoagulable state[16]. Rifampicin and isoniazid appear to accelerate this response[16]. Moreover, rifampicin causes dysregulation of coagulant factors and increases anticoagulant clearance[17]. In South Africa over 60% of TB patients are co-infected with HIV[14] and most will receive ART with TB treatment at some stage during their treatment for TB[18, 19].

Traditional risk factors known to increase the risk of VTE include obesity[20,21], smoking[20], malignancy, prolonged travel (> six hours) [22], use of contraception[23], pregnancy and the puerperium (up to 28 days post-partum) [24], prolonged immobility[25], recent major surgery, and paraparesis or orthopaedic cast of a limb.

In high HIV and TB burdened settings, VTE therapy is complicated by drug-drug interactions between coumadin-based treatments for VTE. Warfarin co-administered

with rifampicin[26-29], non-nucleoside reverse transcriptase inhibitors and protease inhibitors[29-31] make monitoring and management of patients with VTE complex for both the patient and the clinical service. Newer anticoagulants like dabigatran and rivaroxaban require less monitoring and are said to have fewer drug interactions in those receiving therapy for TB or HIV; however this requires more extensive investigation [30, 32, 33]. Some studies have shown these agents to be as effective and cost effective in high income countries[34].

The Wells' pre-test probability score for DVT [35, 36] and PE[37, 38] is used to estimate the probability of a PE or DVT. The presence of specific clinical parameters contribute to a composite score; low scores imply a low probability[39] and high scores an increased probability for VTE, which suggest further investigation is required. However, few studies have reported Wells' scores in patients from sub-Saharan Africa. Evidence or history of either HIV-infection or TB disease is not part of the Wells' scoring system. We therefore prospectively evaluated new onset VTE in our setting of high HIV/TB co-infection, comparing clinical characteristics by HIV status, and the presence or absence of TB disease, and calculated the Wells' scores in all patients.

Methods

Ethical approval was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (Certificate M15740).

A cohort of adult in-patients diagnosed with VTE from September 2015 to May 2016 were recruited prospectively at Tshepong Hospital, North West Province from September 2015-May 2016. All patients aged 18 years and older with a radiologically confirmed DVT or PE were approached to participate. Deep vein thrombosis was confirmed by Doppler ultrasound of the affected limb illustrating at least one of the following: presence of a thrombus, non-compressibility or diminished venous flow [2]. Pulmonary embolism was confirmed by computed tomography pulmonary angiogram (CTPA) showing a filling defect(s) or embolus seen in the pulmonary artery/arteries [40]. To identify patients, radiology records were reviewed daily and those diagnosed with VTE were approached. Written informed consent for participation in the study was obtained.

Patients were interviewed and clinical and laboratory data were obtained from routine hospital records – all in-patients are offered HIV-testing routinely following

pre-test counselling. Interviews involved documentation of risk factors for VTE. In all patients, smoking and travel history (prolonged air or road travel >six hours) within the last four weeks. In women a history of injectable or oral hormonal contraceptive use within the last 3 months and current and recent pregnancy were recorded. Patient's HIV status, antiretroviral therapy (ART) details including onset and duration, any defaulting period (longer than two months), as well as most recent viral load and CD4 cell count were documented. Diagnosis of active TB, site, initiation of treatment, its duration and type were documented. Weight and height were documented in order to calculate body mass index (BMI). Wells' score for pulmonary embolism and deep vein thrombosis was calculated for each patient. Collateral non-varicose veins, localized tenderness, swelling and/or pitting oedema of the entire affected limb and calf swelling more than three cm in the symptomatic limb were noted[35]. In those with a PE, the electrocardiogram (ECG) was analyzed for features of sinus tachycardia and right ventricular strain: $S_1Q_3T_3$ pattern and tall R-wave in standard lead V_1 with non-specific T wave changes in anterior leads[41].

Frequencies and percentages were calculated for categorical variables. Continuous data were assessed for normality and where data were non-normal, medians and interquartile ranges (IQR) were determined. The results were stratified by overall HIV status, HIV/TB co-infection and HIV only (without TB infection). Chi-square or Fisher's exact test was used to determine the association between categorical variables and t-test or Kruskal-Wallis test was used to compare the continuous variables. P-values were obtained for all variables considered. Variables with p-value less than or equal to 0.05 were considered as significant. Statistical analysis was perfomed using SAS Enterprise Guide 7.1.

Results

One hundred and twenty five adult patients were diagnosed with VTE at Tshepong Hospital over the study period; 100 inpatients were consented to participate in the study. These patients comprised 1.5% of all adult medical admissions (6,777 patients) to the hospital over the study period. Those not recruited (25 patients) were either diagnosed and treated as outpatients, or were referred to other hospitals for treatment.

Deep vein thrombosis was diagnosed in 83 patients, PE in 11 patients and six had both a PE and DVT. In those with a DVT, 84 (94.4%) had a unilateral limb DVT, whilst 12 (13.5%) had bilateral lower limb DVT's. Of the 17 patients with a PE, 11 patients (64.7%) had bilateral lung involvement. Sixty seven patients were women. Overall, the median age was 47.0 years (IQR 35.0-57.0). The median BMI of the cohort was 23.3 (IQR 19.9-31.0) from 96 patients from whom the measurements were obtainable (see Table 1). The median Wells' score for all DVT patients was 3.0 (IQR 1.0-4.0). The median Wells' score for all PE patients was 3.0 (IQR 2.5-4.5). Sinus tachycardia was the most common ECG finding (eight patients, 47.0 %). Nine patients died during hospitalisation, their median duration of admission was 25.0 days (IQR 20.0-31.0); three were women. All those who died had a DVT only. The median duration of admission for discharged patients was 12.5 days (IQR 6.0-18.0) with a p value of 0.216 comparing HIV positive and HIV negative patients.

HIV and VTE

Fifty nine of 100 patients were HIV-infected, their median age was 40.0 years (IQR 32.5 -50.0); 41 (69.5%) were women. Of the HIV positive patients, 53 (89.8%) had a DVT, 4 (6.8%) a PE and 2 (3.4%) both a PE and DVT. Recent viral load results were available for 38 (64.4%) patients; 11 (28.9%) were virally suppressed (viral load less than 50 copies/mL); 20 had a viral load 50-1000 copies/mL (52.6%), and 18 (47.3%) a viral load >1000 copies/m. Fifty-seven patients (96.0%) had CD4 counts available; their median CD4 count was 130.0 cells/μL (IQR 58.0-351.0). Thirty four patients (59.7%) had a CD4 count below 200 cells/μL, 26 of these being HIV/TB co-infected compared to those with HIV infection alone (p=0.0002). Those who were HIV positive without TB had a higher median CD4 count of 352.0 cells/μL (IQR: 142.0-451.0) than those with TB (p=<.0001) (see Table 1).

Forty four (74.6%) patients had been initiated on ART prior to VTE diagnosis and one after diagnosis. One patient could not recall (no documentation) when they initiated ART. The median duration on ART was 327.0 days (IQR 60.0 -1601.5 days) (see Table 2). Eighteen (40.9%) patients had started ART within six months (see Figure.1), with 14 of this group having TB co-infection). The majority of patients were receiving a fixed dose combination (FDC) of tenofovir, efavirenz and emtricitabine[18]. Only four patients were receiving protease inhibitors.

Of the HIV-seronegative patients, 26 (63.4%) were women. Thirty seronegative patients had a DVT, seven a PE and 4 had both a DVT and PE. Patients who were HIV negative were older than seropositive patients, with a median age of 56.0 years (IQR: 47.0-64.0) versus 40.0 years (IQR: 32.0-51.0) (p=<0.0001).

Tuberculosis

Overall 39 of 100 VTE patients had TB, 24 with laboratory confirmed TB; 29 had evidence of pulmonary TB. Most (32 patients, 82.0%) patients were co-infected with HIV. The median age in this group overall was 39.0 years (IQR 32.0-47.5).The HIV/TB co-infected patients had a median age of 39.0 years (IQR 32.0 -43.5) compared to those with TB infection alone at 53.0 years (IQR 31.0-60.5) (p=0.35).

The median CD4 count of HIV/TB co-infected patients was 75.5 cells/μL (IQR 38.0-135.0), with a median VL of 106 564.0 copies/mL (IQR 250.5-431016.0). Twenty five patients were on ART; only two were virally suppressed (see Table 1).

Thirty eight patients were already on TB treatment prior to VTE diagnosis (one patient started after diagnosis). The median duration on TB treatment was 27.0 days (IQR 5.0-62.0) (see Table 2). Venous thromboembolism was diagnosed in 20 (52.6%) patients within the first month of initiating rifampicin-based TB treatment and of those, 16 within two weeks of initiating TB treatment (Figure 2). Within this group of 20 patients, six were HIV negative. Ten of the 14 HIV/TB co-infected patients were on ART; 5 of which were on ART for < six months. Twenty-nine (76.3%) patients were in the intensive phase of TB treatment[19]. Four patients were on treatment for drug resistant TB. Over the study period, 1236 (18.2%) of the adults admitted to the medical wards had a diagnosis of TB.

Wells' score

All sub-groups of patients with a DVT had a median Wells' score of 3.0 (IQR 1.0-4.0) (see Table 1). Pitting oedema in the affected leg, localised calf tenderness and calf swelling more than three cm were the most common parameters seen (61.7%, 56.6% and 48.5% respectively) overall in patients with DVT. In the HIV-infected group (TB included) clinical features differed: pitting oedema greater in symptomatic leg (68.5%), calf swelling more than 3cm (53.7%) and, collateral non-varicose superficial veins (22.2%) were the most common features.

The median Wells' score for all patients diagnosed with PE was 3.0 (IQR 2.5-4.5). The HIV positive only group and HIV/TB co-infected group had the highest Wells' PE scores, with a median score of 3.8 (IQR 3.0.-7.0) and 5.3 (IQR 3.0-7.5) respectively (see Table 1).

Traditional Risk factors

Thirty six patients had a smoking history with 4.0% of women and 8.0% men self-reporting smoking at the time of diagnosis of VTE (current smokers). Twenty seven were obese (BMI above 30 kg/m^2) of whom 10 were HIV-infected. Seven patients had a malignancy (five had Kaposi's sarcoma). Recent major surgery and/or immobilisation were reported by eight patients, and six women were using contraception (see Figure 3).

Discussion

There are few studies in sub-Saharan Africa reporting factors related to HIV and TB in patients with VTE. This study's finding of high HIV and TB prevalence amongst those with VTE suggest that these infections are possibly important risk factors for thromboembolic disease, with therapy for these conditions adding to risk. Nine percent of our sample died after a median time of 25 days after admission, demonstrating both the human and financial cost of this illness to the health system.

We report an overall prevalence of VTE of 1.5% amongst all adults admitted to the medical wards over the study period. Studies in high income countries report two-10 fold increased risk of VTE in HIV positive individuals [7, 42] compared to their HIV negative counterparts. The majority of patients with VTE in our study were HIV-infected, similar to other South African studies[2, 43]. HIV prevalence in our study was markedly higher than the general HIV prevalence in South Africa (12.7%) [13].

The TB prevalence amongst our study population (39.0%) was strikingly higher than the prevalence amongst adults admitted over the study period (18.2%), the majority of whom were HIV co-infected. Other studies in similar hospital settings in South Africa have reported comparable TB prevalence in those with DVT[2, 9]. It has been estimated that three -four% of patients with TB will develop VTE, with the mortality of inpatients with combined VTE and active TB being greater than the risk of TB or VTE alone [44].

The median age of the HIV-infected patients with VTE was younger than the HIV negative patients in our study, although the highest prevalence of HIV in South Africa is in a younger age group (15- 34.9 years) [13]. Premature biological aging seen in younger patients with HIV may add to VTE burden [45]. Women comprised 67.0% of all patients, which is similar to findings in another South African study group and national HIV statistics [9, 13]. Studies carried out in developed settings show, in contrast to ours, a predominance of male patients with VTE[4, 10], possibly reflecting different risks for HIV[46] in our setting where the epidemic predominantly affects women[13, 47].

Severe immunodeficiency was a dominant finding amongst the HIV positive group – indeed, 34 had CD4 count < 200 cells/μL - similar to other studies [3, 8, 25, 40,46,48,49]. Those co-infected with HIV and TB had markedly lower CD4 counts. Interestingly, viral loads were not uniformly high, consistent with other studies, showing no direct association between thromboses and viral load [3, 4, 8, 40].

Forty percent of patients in our study had initiated ART within six months prior to VTE. Levels of markers of endothelial cell dysfunction and coagulation are found to be abnormal in HIV positive patients recently initiated on combined ART therapy [50]. Mjiluf-Cruz et al[51] found the median time to onset of VTE following ART initiation to be 7 months, similar to our study, which suggests that immune reconstitution following ART initiation may be contributing to the onset of VTE. Immune reconstitution in the form of an increase in CD4 and CD8 T lymphocyte cell count occurs in the first three - six months following ART initiation [52]. This may lead to increased circulating pro-inflammatory markers and activation of the inflammatory cascade resulting in a prothrombotic state. However, others have not reported similar findings[4, 53].In our study most of those who were initiated on ART and developed VTE early also had TB co-infection. Only four of those whom developed VTE soon after ART initiation did not have TB co-infection, make it difficult to largely attribute ART to the cause of hypercoagulable state in this group. Of the 12 patients in our study diagnosed within three months of initiating ART, nine had co-existent TB, suggesting VTE IRIS following ART may be exacerbated by the thrombotic risks of TB and its treatment. Numerous studies have shown the correlation of protease inhibitor containing regimens [51, 54, 55] and the onset of VTE. In our study, only four patients were on a PI containing regimen, making it difficult to comment.

Tuberculosis has been found to create a hypercoagulable state due to various mechanisms [16, 17, 44, 56, 57]. Anti -TB treatment also contributes to the risk for VTE, particularly two weeks after initiating rifampicin[17]. This is similar to our study where most VTE episodes in TB patients occurred within the first month of starting TB treatment. Importantly, most of the patients who were on TB treatment only (HIV negative) presented within one month, alluding to an immune reconstitution related hypercoagulable state following the initiation of TB treatment.

Patients with a BMI > 30 kg/m^2 were predominantly HIV seronegative, possibly suggesting that obesity is not a predisposing factor in HIV-infected adults[9]. Our study found only six patients had a ≥20 pack year smoking history. Smoking has been shown to carry a risk for VTE [58, 59] in conjunction with other risk factors such as HIV [4]. Seven patients in our study had cancer, five of whom had HIV-related Kaposi's sarcoma (8.5% of HIV positive group). This differs from another South African study which reported malignancy more frequently in HIV negative patients[43]. Crum–Cianflone *et al* similarly found 6.0% of HIV-infected adults with VTE to have cancer[4]. Kaposi's sarcoma is related to VTE development due to vessel compression and infiltration[48]. Eight patients were recently immobile or had recent major surgery with only 4 being HIV positive, illustrating the independence of these risk factors for VTE. Only six patients were on contraception, mainly the injectable type, creating additive risk[24].

The Wells' scores for those with a DVT was the same in all the HIV and/or TB sub-groups. The Wells' score calculated for those with a PE and HIV infection was 3.8 (moderate probability) which was lower than the HIV/TB co-infected group; however the number in this patient group was smaller. In each HIV/TB subgroup, scores suggested moderate to high probability for VTE but HIV/TB co-infected patients did not appear to have significantly higher Wells' score for DVT. More research is needed to assess a modification to the Wells' score that incorporates HIV sero-status and TB disease status – and possibly duration of therapy.

This study has several limitations. We relied on routinely collected data – which was missing in several patients. We did not include controls without VTE, making it difficult to assess the validity of Wells' score in HIV and HIV/TB co-infected patients. Measures of coagulation were not routinely done; D-dimers were not measured in a

large proportion and thus we have not reported on these values. However, D-dimers are used for their negative predictive value, and all our cases were proven radiologically.

Multiple prior studies report that HIV and TB each separately pose an increased risk for acquiring VTE. Our study illustrates the apparent contribution that both HIV, TB and their therapies confer on incident VTE, as well as a possible immune reconstitution related hypercoagulable state soon after starting ART and/or anti-TB therapy. Further studies are warranted to assess whether thrombo-prophylaxis would counter the hypercoagulable state that may exist in HIV-infected patients with TB, receiving rifampicin treatment as many patients in our study were ambulatory with no other risk factors for VTE. The high burden of both HIV and TB in sub-Saharan Africa suggests that closer study of VTE is required, especially for novel preventive strategies in HIV/TB co-infected patients and also for therapy.

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Figures/Tables

Table 1. Overall summary of demographics, diagnosis, clinical and laboratory findings stratified by HIV and TB infection

		HIV-infected		HIV-seronegative	
	Overall	TB infected	No TB	TB infected	No TB
Number	100	32	27	7	34
Age (years)					
Median (IQR)	47.0 (35.0-57.0)	39.0 (32.0-43.5)	44.0 (35.0-59.0)	53.0 (31.0-60.5)	56.0 (48.0-65.0)
Gender					
Female (%)	67 (67.0)	22 (68.8)	19 (70.4)	4 (57.1)	22 (64.7)
Body mass index					
Obese (%)	27/96 (28.1)	0/30 (0.0)	10/26 (38.5)	0/7 (0.0)	17/33 (51.5)
Median (IQR)	23.3 (20.0-31.1)	20.1 (17.0-22.9)	24.1 (21.2- 32.0)	21.6 (21.1-23.4)	30.7 (23.3-38.2)
Diagnosis					
DVT (%)	83 (83.0)	30 (93.8)	23 (85.2)	4 (57.1)	26 (76.5)
PE (%)	11 (11.0)	1 (3.1)	3 (11.1)	2 (28.6)	5 (14.7)
DVT and PE (%)	6 (6.0)	1 (3.1)	1 (3.7)	1 (14.3)	3 (8.8)
Wells score (DVT)	n=89	n=31	n=24	n=5	n=29
Moderate risk (%)	23 (25.8)	9 (29.0)	7 (29.2)	1 (20.0)	6 (20.7)
High risk (%)	64 (71.9)	22 (80.0)	17 (70.8)	4 (80.0)	21 (72.4)
Median (IQR)	3 (1.0 – 4.0)	3 (1.0 – 3.0)	3.0 (1.0 – 4.0)	3 (2.0 – 3.0)	3 (1.5 – 4.0)
Wells score (PE)	n=17	n=2	n=4	n=3	n=8
Moderate (%)	9 (52.9)	1 (50.0)	2 (50.0)	1 (33.3)	5 (62.5)
High risk (%)	3 (17.7)	1 (50.0)	1 (25.0)	0 (0.0)	1 (12.5)
Median (IQR)	3 (2.5-4.5)	5.25 (3.0-7.5)	3.8 (2.3-5.8)	1.5 (1.5-4.5)	3 (3-4.5)
CD4 count (cells/mL)					
Less or equal to 200 (%)	34(59.7)	26/32 (81.3)	8/25 (32.0)*	-	-
More than 200 (%)	23 (40.35)	6/32 (18.8)	17/25 (68.0)*	-	-
Median (IQR)	130.0 (58.0-351.0)	75.5 (38.0-135.0)	352.0 (142.0-451.0)	-	-
Viral load (copies/mL)					
Median (IQR)	968.5 (0.0-128 961.3)	106 564.0 (250.5-431 016.0)	968.5 (0.0-128 961.3)	-	-
Viral suppression (n)	11/38**	2/19	9/19		

*Only 25 out of 27 CD4 counts available
**Only 38 viral load results available

Table 2. Factors related to HIV treatment and TB treatment according to HIV positive and HIV negative sub groups.

		HIV-infected		HIV-seronegative	
	Overall	TB infected	No TB	TB infected	No TB
Number on ART therapy	45 (76.3)	25 (78.1)	20 (74.1)	-	-
Time on ART therapy (days) Median (IQR)	327.0 (60.0-1601.5)	129.5 (39.5-716.0)	1023.5 (197.5-2684.0)	-	-
Number on TB treatment	39	32	-	7	-
Time on TB treatment (days) Median (IQR)	27.0 (5.0-62.0)	40.5 (7.0-70.0)	-	6 .0 (2.0-13.0)	-

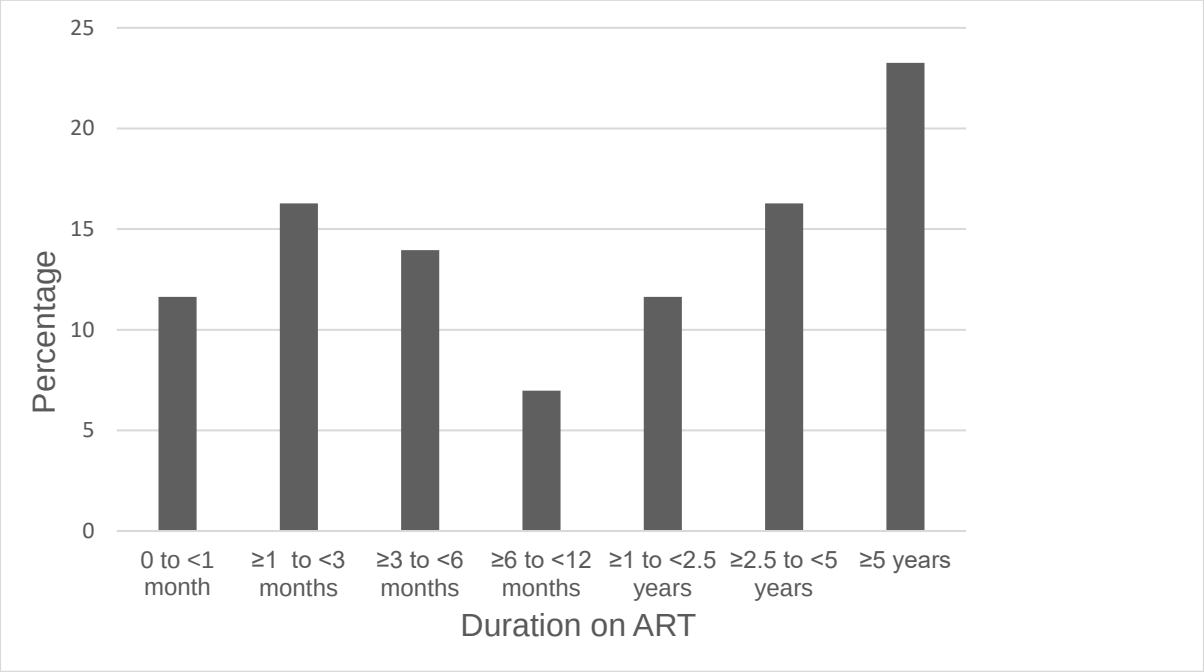


Figure 1. Patients grouped according to duration of ART prior to onset of VTE (n=43)

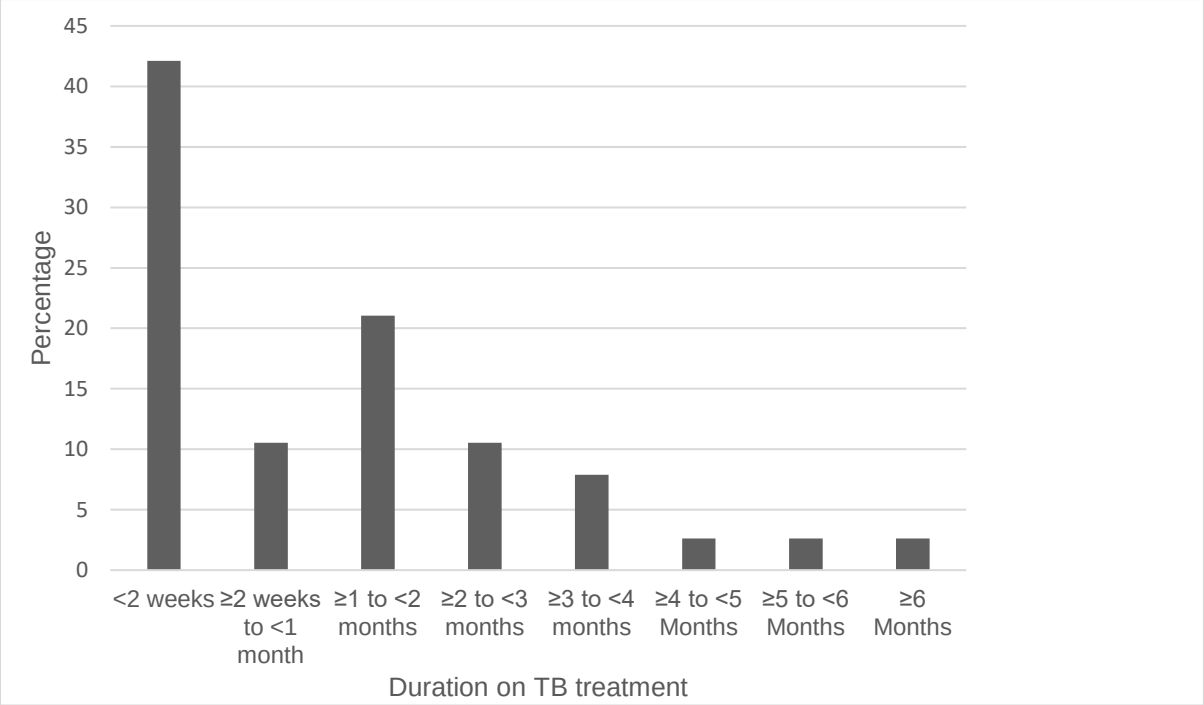


Figure 2: Patients grouped according to duration of TB treatment prior to onset of VTE (n=38).

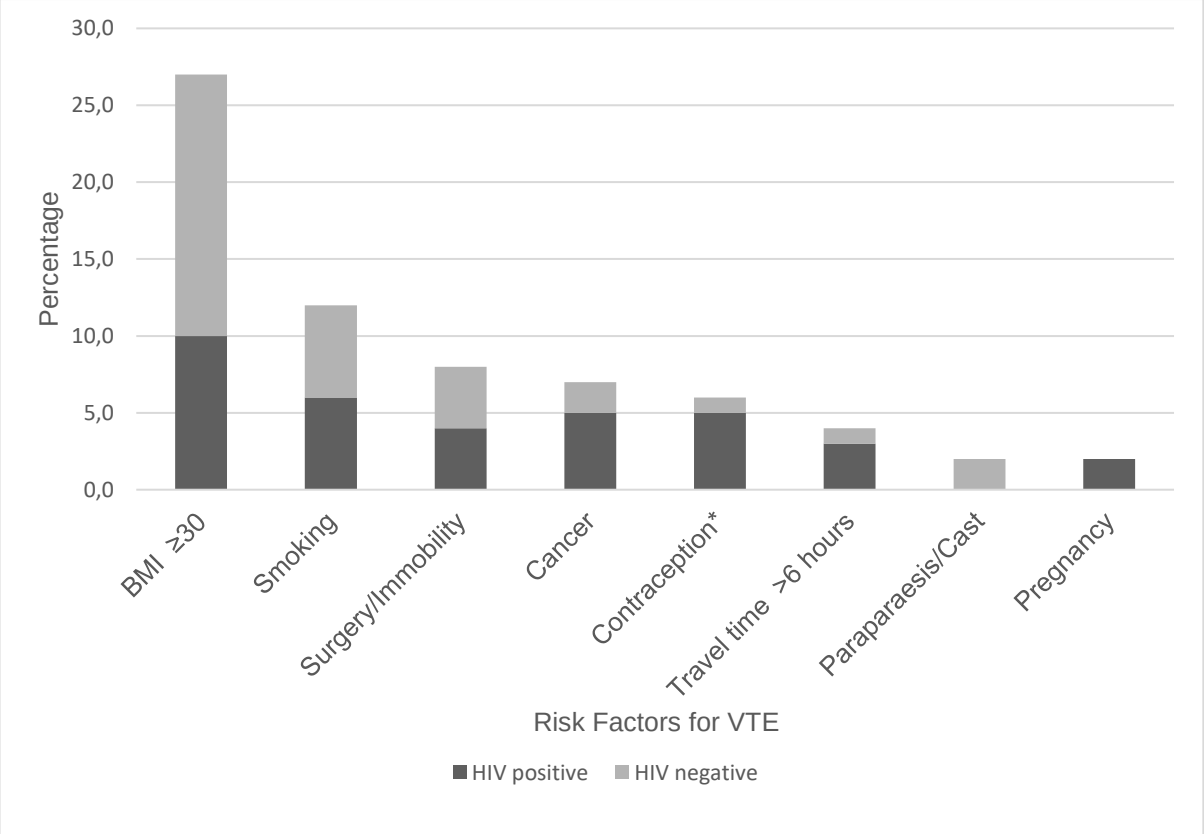


Figure 3: Percentage of study population with traditional risk factors for VTE according to HIV status (n=100)

CHAPTER 3- APPENDICES

3.1 Data Collection Sheet

Study code: __ __ __ __
Age __ __ __
Date of birth (DD/MM/YYYY): 15 / __ __ / __ __ __ __

Date of admission (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

Outcome: □ Discharged □ Hospital death

Date of discharge/death (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

Diagnosis □ Deep Vein Thrombosis □ Pulmonary Embolus

Gender
□ Male □ Female

Race
□ African □ Caucasian □ Indian □ Coloured □ Other

Weight (kg): __ __ __
Height (cm): __ __ __

Symptoms of DVT

- Localised tenderness □ Yes □ No
  Hours: __ __ Days: __ __ Weeks __ __

- Swelling of entire leg □ Yes □ No
  Hours: __ __ Days: __ __ Weeks __ __

Symptoms of PE

- Acute shortness of breath □ Yes □ No
  Hours: __ __ Days: __ __ Weeks __ __

- Acute chest pain □ Yes □ No
  Hours: __ __ Days: __ __ Weeks __ __

- Dizziness/sudden collapse □ Yes □ No

  Hours: __ __ Days: __ __ Weeks __ __

- Haemoptysis □ Yes □ No

Hours: __ __ Days: __ __ Weeks __ __

- Symptoms of DVT □ Yes □ No

Smoking history

Have you ever smoked tobacco □ Yes □ No
(Tobacco includes pipes, hand rolled cigarettes)
If yes, how old were you when you started smoking: __ __
Are you still smoking □ Yes □ No?
If no:

- Did you stop in the last 6 months □Yes □No
  - If no, how old were you when you stopped smoking: __ __ __

How many cigarettes do/did you smoke per day: __ __?

Travel history

Have you travelled anywhere in the last 4 weeks: □ Yes □ No

- If yes
  - How long ago did you travel: __ __ hours __ __ days __ weeks
  - Was the trip more than 6 hours long: □ Yes □ No

Major surgery (within the last 4 weeks) and immobility

□ Intra-abdominal
□ Extensive bone/joint
□ Surgery lasting more than 45 minutes Area: _____
□ Immobile/bed ridden for last 3 days

Pregnancy (females only)

- Are you currently pregnant: □ Yes □ No
- If yes:
  - □ <12 weeks
  - □ 12-20 weeks
  - □ >20 weeks
- If no, were you pregnant in the last 28 days: □ Yes □ No

Contraception

- Have you used any form of contraception in the last 3 months: □ Yes □ No
- If yes, what kind: □ Injection □ Tablet □ Implants

Immobility

- Carnovsky score: __ __ __
  - □ Orthopaedic casting lower extremities
  - □ Currently paralysed
  - □ Currently paretic

Active cancer

Cancer currently being treated □ Yes □ No

Cancer treated within the last 6 months □ Yes □ No
Currently receiving palliative care □ Yes □ No
Site of cancer_____

Previous DVT/PE □ Yes □ No

Patient examination

- □ Localised tenderness
- □ Swelling of entire leg
- □ Calf swelling 3cm greater than other leg
- □ Collateral non-varicose superficial veins
- □ Pitting oedema greater in symptomatic leg

HIV/AIDS

HIV status: □ Positive □ Negative □ Unknown

Is the patient on ART: □ Yes □ No □HIV NEGATIVE?

For HIV positive patients:

Date of diagnosis: __ __/ __ __ / __ __ __ __

If patient not on ART: □ Never on ART □ Defaulted

If defaulter, when (MM/YYYY): _____

- Restarted □ Yes □ No
  - If yes, when (MM/YYYY): _____

If the patient is on ART, ART history

	Date started (DD/MM/YYYY)	Date most recently stopped (DD/MM/YYYY)	Date most recently initiated (DD/MM/YYYY)
□ Odimune/Tribuss/Atrozia (FDC)	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __
□ Tenofovir (TDF)			
□ Stavudine (d4T)	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __
□ Zidovudine (AZT)	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __
□ Lamivudine (3TC)	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __	__ __/ __ __ / __ __ __ __

□ Emtricabine (FTC)	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __
□ Efavirenz (EFV)	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __
□ Aluvia	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __
□ Abacavir (ABC)	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __
□ Other (specify): _____	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __	__ __/__ __ /__ __ __ __

Recent CD4: _____ □ No CD4 available

- Date of CD4 (MM/YYYY): _____
- Result: _____

Recent Viral Load: _____ □ No Viral Load available

- Date of viral load (MM/YYYY): _____
- Result:_____

Tuberculosis (TB)

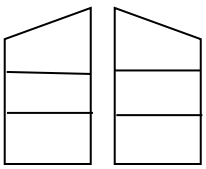
Does the patient currently have TB? □ Yes □ No □ Unknown

If patient has TB:

- Date of initiation of treatment (MM/YYYY):_____

- Type of TB
  - □ Pulmonary
    - GXP □ Rif sensitive □ Rif resistant □ No GXP sent
    - Culture □ Positive □ No culture sent
    - AFB □ Positive □ No AFB sent
    - LPA result: _____ □ No LPA sent
    - Empiric □ Yes □ No
    - Chest X-ray: □ Normal □ Cavitations
      □ Miliary □ Infiltrate
      □ Effusion □ Adenopathy
      □ Bilateral disease

No of zones involved (or CXR) ___/6



  - □ Abdominal
    - □ Sonar
    - □ Biopsy
  - □ Meningitis

- Lymph-adenitis
  - Biopsy done □ Yes □ No
  - AFB □ Positive □ No AFB sent
  - GXP □ Rif sensitive □ Rif resistant □ No GXP sent
  - Culture □ Positive □ No culture sent
- Bone marrow
- Other: _____

- Treatment

	Date Started (MM/YYYY)
□ Rifafour	__ __ / __ __ / __ __ __ __
□ Rifinah	__ __ / __ __ / __ __ __ __
□ Rifampacin	__ __ / __ __ / __ __ __ __
□ Isoniazid	__ __ / __ __ / __ __ __ __
□ Pyrazinamide	__ __ / __ __ / __ __ __ __
□ Ethambutol	__ __ / __ __ / __ __ __ __
□ Moxifloxacin	__ __ / __ __ / __ __ __ __
□ Kanamycin	__ __ / __ __ / __ __ __ __
□ Amikacin	__ __ / __ __ / __ __ __ __
□ Terazidone	__ __ / __ __ / __ __ __ __
□ Ethionamide	__ __ / __ __ / __ __ __ __

D-dimer:

- □ Yes, result: _____
- □ No

Troponin done (for pulmonary embolus)

- □ Yes, result: _____
- □ No

ECG (pulmonary embolism)

- □ Normal
- □ Sinus tachycardia (>100 beats per min.)
- □ S1-Q3-T3
- □ Tall R-waves in lead V1
- □ Tall, peaked P-waves in lead II
- □ Right axis deviation
- □ Right bundle branch block
- □ Non-specific T wave changes
- □ Not done

Doppler ultrasound findings

Doppler ultrasound done □ Yes □ No
Date (DD/MM/YYYY): __ __/__ __/__ __ __ __

Site

- ☐ Arm ☐ Leg
- ☐ Right side ☐ Left side ☐ Both sides
- ☐ Proximal veins ☐ Distal veins ☐ Popliteal veins

Findings

- ☐ Thrombus
- ☐ Decreased compressibility
- ☐ Decreased/absent blood flow

CT Pulmonary Angiogram findings

CT done ☐ Yes ☐ No
Date (DD/MM/YYYY): __ __/__ __/__ __ __ __

Site

- ☐ Right lung ☐ Left lung ☐ Both lungs
- ☐ Proximal branches ☐ Distal branches

Findings

- ☐ Thrombus
- ☐ Filling defect
- ☐ Other pulmonary infiltrates

Other diagnosis less likely than PE ☐ Yes ☐ No

Other diagnosis more likely than DVT ☐ Yes ☐ No

Well's score for Pulmonary Embolus: __ __

Well's score for Deep Vein Thrombosis: __ __

3.2 Ethics approval

R14/49 Dr Pramodhini Moodley

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150740

NAME: (Principal Investigator)	Dr Pramodhini Moodley
DEPARTMENT:	Internal Medicine Tshepong Hospital, Klerksdorp, North West
PROJECT TITLE:	Descriptive Study of Venous Thromboebolic Disease in the Adult Population Admitted to Tshepong Hospital Comparing the Proportion of HIV and Non-HIV Infected Patients
DATE CONSIDERED:	31/08/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Neil Martinson and Ebrahim Variava
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/09/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

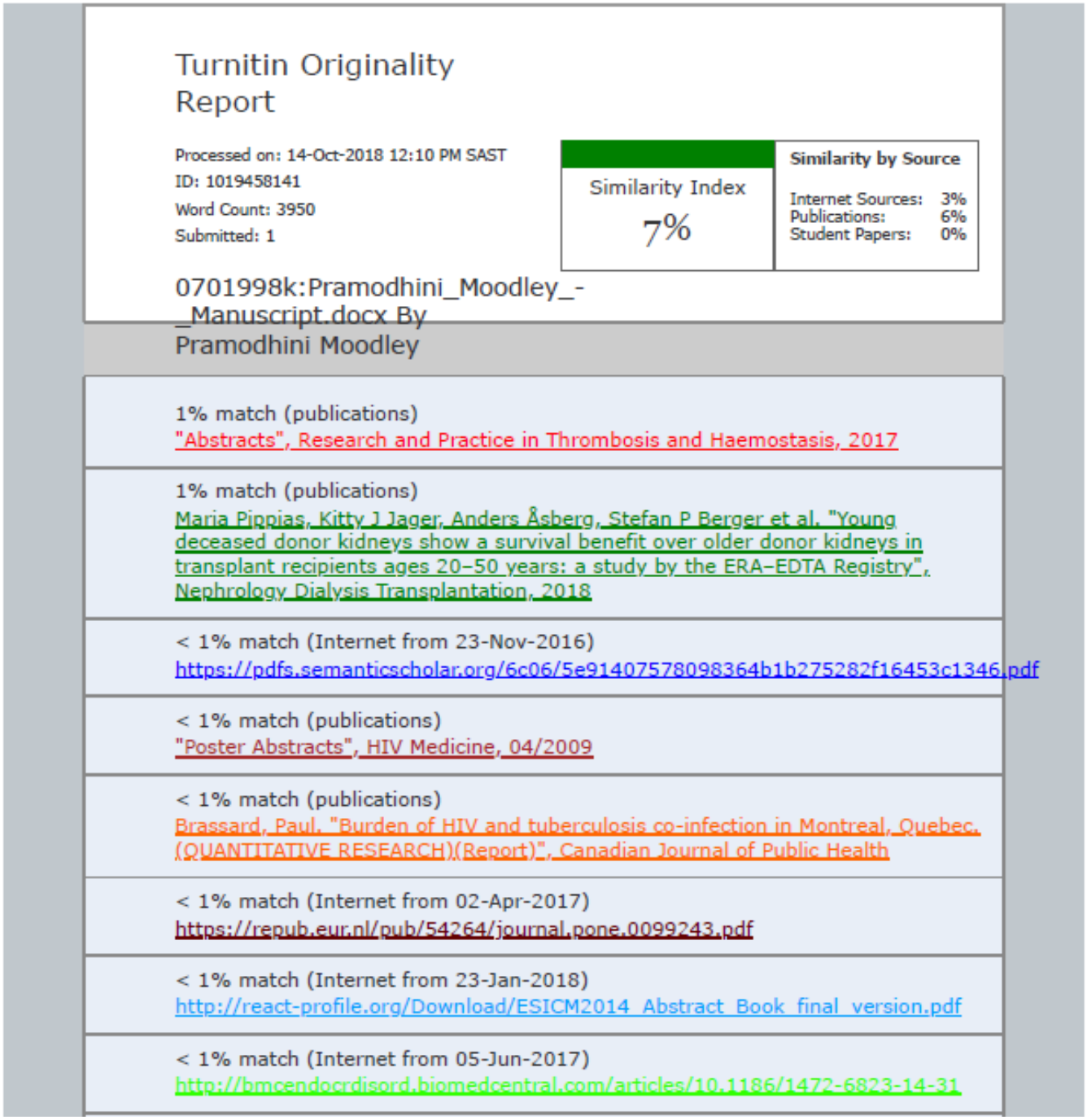
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.3 “Turn it in” Report



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