Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–9

DOI: 10.1177/0956462414561033
std.sagepub.com

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Venous thromboembolism among HIV positive patients and anticoagulation clinic outcomes integrated within the HIV primary care setting

Riddhi A Modi[1], Gerald McGwin[2], Andrew O Westfall[3], Deon W Powell[1], Greer A Burkholder[1,4], James L Raper[1,4] and James H Willig[1,4]

Summary

The purpose of this study was to explore factors associated with venous thromboembolism (VTE) among a cohort of HIV-infected patients and to describe early outcomes of warfarin anticoagulation therapy (WAC) treated in a pharmacist-based anticoagulation clinic (ACC). A nested case control study was conducted using the University of Alabama at Birmingham (UAB) 1917 HIV Clinic Cohort. Conditional logistic regression (CLR) was used to estimate factors associated with VTE. Among HIV-infected VTE cases, ACC managed patients were compared to primary care provider (PCP) managed patients to determine Time within Therapeutic INR Range (TTR). CD4 < 200 cells/μl (OR = 4.50; 95% CI = 1.52, 13.37; $p = 0.007$) and prior surgical procedures (13.20; 1.56; 111.4; $p = 0.018$) demonstrated positive associations with VTE, whereas longer HIV duration demonstrated a negative association (0.87; 0.78, 0.98; $p = 0.019$). TTR was 56.2% among ACC managed patients compared to 30.5% of PCP managed patients ($p = 0.174$). Overall, prior surgical procedures and low CD4 count were associated with an increased risk of VTE among HIV-infected patients. Despite small sample size, patients managed in ACC tend to achieve greater proportion of TTR compared to those managed by PCPs, suggesting that this model of therapy may provide additional benefits to HIV-infected patients.

Keywords

HIV, thrombosis, anticoagulation outcomes, matched case control, conditional logistic regression

Date received: 28 August 2014; accepted: 30 October 2014

Introduction

Due to potent combination antiretroviral therapy (ART), HIV has changed from a life threatening illness to a treatable chronic infection, with over a million people currently living with HIV/AIDS (PLWHA) in the USA.[1–4] With longer life expectancies, new challenges such as increased co-morbid illness now affect PLWHA.[5–7] In particular, the rates of venous thromboembolism (VTE), including deep venous thromboses (DVT) and pulmonary embolisms (PE) remains common and some report that they are increasingly common.[3,8–14] The risk of thromboembolism among PLWHA is thought to be due to a variety of acquired and genetic factors including a hypercoagulable state due to an abnormal coagulation cascade.[2,9,14–21] Thus far, studies of thrombosis risk among PLWHA[8,14,20,22] consist of small prospective and/or retrospective cohort studies or limited case-control studies.[2,8,9,13,15,21]

For HIV patients diagnosed with VTE, warfarin anticoagulation (WAC) with serial monitoring of international normalized ratios (INR) to gauge

[1]Division of Infectious Diseases, University of Alabama at Birmingham (UAB), Birmingham, AL, USA
[2]Department of Epidemiology, School of Public Health, UAB, Birmingham, AL, USA
[3]Department of Biostatistics, UAB, Birmingham, AL, USA
[4]University of Alabama School of Medicine (UAB), Birmingham, AL, USA

Corresponding author:
Riddhi Modi, CCB 178, 908 20th Street South, Birmingham, AL 35294-2050, USA.
Email: rmodi@uab.edu

the effectiveness of anticoagulation is the standard of therapy.[23–25] Due to variable dose response associated with drug interactions, diet, and other comorbid conditions, providers must monitor INR values frequently and adjust WAC dosing as needed to consistently maintain the recommended therapeutic window.[3,23,25–28] There is great variability in how each provider adjusts warfarin dosage, which affects overall treatment outcomes.[29]

Pharmacist-managed anticoagulation clinics (ACC) represent an alternative to primary care provider (PCP) managed anticoagulation and have demonstrated efficient INR control and improved patient care among the general population being treated for thrombosis.[23,26–28,30,31] Benefits include reduced mortality, reduced number of hospitalizations and emergency visits, and superior quality of anticoagulation.[27,30] Proportion of Time within Therapeutic INR Range (TTR) is one of the quality markers to measure the effectiveness of WAC therapy.[32,33] There are limited published data gauging the impact of the pharmacist-managed ACC strategy among warfarin-managed VTE cases in the HIV outpatient setting. In this study, we explore factors associated with VTE among PLWHA as well as describe therapy outcomes of those patients treated by PCPs versus a pharmacist-managed ACC strategy.

Methods

Setting and study population

The UAB 1917 HIV Outpatient Clinic is home to the UAB 1917 Clinic Cohort Observational Database Project, an Institutional Review Board (IRB) approved ongoing prospective clinical cohort study ($n \geq 4400$ enrolled since 1995) with detailed socio-demographic, psychosocial, and clinical information. Annually, more than 2500 patients receive primary and sub-specialty HIV care at the clinic. A locally developed electronic health record (EHR) was used from 2004 until 2012 which imported all laboratory values from the central UAB laboratory, required electronic prescription for all medications and contained detailed provider encounter notes. The EHR and database were quality controlled, with all provider notes reviewed to ensure appropriate data capture regarding changes (additions or deletions) in diagnoses, allergies and medications, including start and stop dates for antiretroviral and all other prescribed medications.[5,6,34] The UAB IRB approved this nested case control study within the UAB 1917 Clinic Cohort. All patients aged 19 years and older who had at least one primary HIV care visit at the UAB 1917 Clinic between January 1, 2000 and December 31, 2011 were eligible for participation in this study.

The 1917 anticoagulation clinic

The 1917 Anticoagulation Clinic is a pharmacist-managed sub-specialty clinic started in 2009 to help with the management of anticoagulant therapy in the UAB 1917 HIV primary care clinic setting. The 1917 ACC operates under the direction of a physician (JW) and is staffed by four pharmacists who rotate on a monthly basis. The ACC only accepts referrals from UAB 1917 Clinic providers for patients who require either initiation or maintenance of WAC. At the time of referral, a form which details diagnosis, length of therapy and target INR range is completed and signed by the requesting provider. At the initial visit, pharmacists collect detailed socio-demographic and anticoagulation history along with information on other medications to review potential side effects. Patient education on WAC compliance, routine INR monitoring, side effects, dietary requirements and warfarin interactions is an integral part of the visit. For every visit, pharmacists document a detailed template EHR note. Patients are discharged from the clinic when they no longer need WAC therapy, when the referring provider requests discharge, when a well-controlled patient ''graduates'' to home INR monitoring, or non-compliance with appointments (three or more missed visits). Details on anticoagulation visits, warfarin dose and INR measurements were collected through medical chart review (RM).

Study design – risk for VTE outcome

Cases. Patients with a diagnosis of venous thrombosis (DVT and/or PE) in their electronic medical record were identified through a query of our database. VTE was confirmed with individual patient chart review (RM). Medical chart review included reviewing provider notes available on EHR for participants. If a patient had multiple episodes of VTE, only the first episode after HIV diagnosis was considered for this study.

On the initial electronic query, 67 patients were identified as having a VTE. Upon chart review, a diagnosis of VTE was not confirmed in three cases, four did not have a VTE diagnosis date, five had multiple VTEs with no information on the first episode and ten had a past history of VTE with no details of or VTE diagnosis before HIV diagnosis. Due to insufficient data, we were unable to utilize these cases in subsequent analyses. Thus, a total of 45 cases met study criteria.

Controls. The incidence density sampling method (selects at risk controls who survived as long as the index case in the risk set) was used to select controls.[35] Controls were matched to cases individually when their initial primary care visit dates occurred within a predefined window (±4 weeks) with a 4:1 ratio. Details of incidence density sampling method can be found elsewhere.[35]

Independent variables

Data were collected via an electronic query of the database (MS SQL). We included patient demographics (age at VTE, gender, race), HIV-associated values [HIV duration, CD4 count and viral load (VL) at or closest to VTE diagnosis, maximum VL value (max VL) and nadir CD4 count prior to VTE diagnosis]; predisposing conditions [all malignancies (AIDS and Non-AIDS), opportunistic infections (OIs), hypertension, diabetes mellitus, cardiovascular disease (CVD, including history of acute coronary syndromes, heart failure), lipid disorders, surgical procedures] and medications (oral contraceptive pills and hormonal replacements used) included in our dataset. Other clinical history was included (depression, tobacco use, substance use and alcohol use). AIDS-related malignancies (per CDC guidelines) were included as malignancies under OI.[36,37] All surgical procedures prior to VTE diagnosis were included.

Statistical Analysis

Factors associated with VTE. Cases and controls were compared with respect to demographics, HIV-related factors and other comorbidities using medians and interquartile ranges (25th and 75th percentiles), and counts and percentages for continuous and categorical variables, respectively (Table 1).[38] To account for the 1:4 matched case-control design, conditional logistic regression (CLR) models were fit for all risk factors to obtain unadjusted and adjusted estimates of the association of each risk factor with a presentation of VTE.

Pharmacist-managed ACC outcomes. All VTE diagnosed cases who were on warfarin therapy managed at our clinic and those who had at least 2 INR values were eligible for the ACC outcomes analyses. The demographic characteristics of those whose WAC was managed by their PCPs ($n = 5$) were compared to those managed by pharmacists in our ACC ($n = 12$) (Fisher's exact test, Wilcoxon rank-sum test). Those participants who were on treatments other than warfarin, or whose anticoagulation was managed by external providers were excluded from these analyses. The INRs for initial 30 days after starting WAC therapy were excluded to allow for initial warfarin dose adjustments and INR stabilization.[27]

The Rosendaal method of linear interpolation was used to calculate "Time within Therapeutic INR Range" (TTR), a surrogate marker of WAC outcomes where the percentage of time a patient's INR was within the therapeutic range. Here, an INR value is allotted for each day between two successive INR measurements to calculate TTR.[39] A percentage of time is calculated where the INR lies within therapeutic range.[33] Participants were followed until completion of WAC therapy, loss to follow up, transfer of care, death or end of study period. An additional end point for ACC patients was a shift to point of care monitoring (home monitoring) where patients independently check and respond to INR values. All statistical analyses were performed using SAS, version 9.3.

Results

Cases ($n = 45$) and controls ($n = 180$) were similar with respect to median age, gender, and race ($p > 0.05$), while the duration of HIV was lesser among cases compared to controls (6.9 vs. 9.5 years; $p = 0.04$). In univariate analysis, cases were more likely to have CD4 counts < 200 cells/μl ($p = 0.0004$), and higher median VL (log 10 copies per ml) compared to controls ($p = 0.02$). Also, cases were more likely to have undergone surgical procedures compared to controls ($p = 0.007$).

In multivariable analysis, CD4 count <200 cells/μl (OR = 4.50; 95% CI = 1.52, 13.37; $p = 0.007$) and prior surgical procedures (13.20; 1.56; 111.41; $p = 0.018$) remained significant predictors of VTE, while median VL (log 10 copies per ml) was no longer independently significant (1.33; 0.90, 1.97; $p = 0.156$) (Table 2). Longer HIV duration (years) was associated with decreased odds of VTE (0.87; 0.78, 0.98; $p = 0.019$). Tobacco use was added to the multivariate model but did not alter the results significantly (data not shown).

To evaluate the WAC outcomes, among the eligible participants with VTE ($n = 17$), those managed by the ACC ($n = 12$) were compared to those managed by their PCPs ($n = 5$). In regards to the impact of our ACC, the median age of the ACC-managed patients ($n = 12$) was 45 and 67% were men (Table 3). The median duration of WAC therapy was lower among ACC-managed patients (138.5 days) compared to PCP managed patients (203 days, $p = 0.499$). ACC-managed patients spent 56.2% of the mean proportion time in therapeutic range (TTR) compared to 30.5% of PCP-managed patients ($p = 0.174$). The median warfarin dose adjustments per patient month was higher among ACC

Table 1. Demographic characteristics for 225 patients receiving HIV primary care at the UAB 1917 Clinic as of December 31, 2011.

Variables	Cases $n = 45$	Controls $n = 180$	p-Value[a]
Demographics			
Age, years	45 (37–52)	43 (37–48)	0.30
Gender			
Male	33 (73.3)	129 (71.7)	0.83
Female	12 (26.7)	51 (28.3)	Ref
Race			
White	22 (48.9)	90 (50.6)	0.81
Black	23 (51.1)	88 (49.4)	Ref
HIV-related factors			
HIV duration, years	6.9 (3.5–11.3)	9.5 (4.5–14.2)	0.04
ART[b]	26 (57.8)	116 (64.4)	0.29
ART type[c] (Yes/No)			
PI	17 (37.8)	65 (36.1)	0.82
NRTI	25 (55.6)	108 (60.0)	0.50
NNRTI	11 (24.4)	62 (34.4)	0.17
II	3 (6.7)	9 (5.0)	0.65
EI	0 (0)	1 (0.6)	0.99
Log_{10} viral load (VL)[d]	2.65 (1.69–4.71)	1.83 (1.69–3.21)	0.02
Detectable VL[e]	23 (71.9)	82 (52.2)	0.06
Maximum Log_{10} VL	5.37 (4.67–5.77)	5.03 (4.41–5.56)	0.35
CD4 count[f], copies/μl of blood	142.5 (17.5–345.0)	419.0 (223.0–40.0)	0.001
CD4 count <200 cells	20 (55.6)	37 (21.8)	0.0004
CD4 count ≥ 200 cells	16 (44.4)	133 (78.2)	Ref
Nadir CD4 count	74.5 (8.0–216.0)	161.0 (29.0–278.0)	0.09
Medical History[g]			
Malignancy	10 (22.2)	28 (15.6)	0.29
Opportunistic infections	16 (35.6)	54 (30.0)	0.48
Hypertension	12 (26.7)	67 (37.2)	0.18
Diabetes Mellitus	18 (40.0)	84 (46.7)	0.42
Lipid Disorder	2 (4.4)	17 (9.4)	0.28
Cardiovascular disorder	3 (6.7)	2 (1.1)	0.05
Surgical Procedures	6 (13.3)	5 (2.8)	0.007
Magestrol use	3 (6.7)	33 (18.3)	0.07
Hormonal Replacement	0 (0)	17 (9.4)	0.99
Depression			
Prior	3 (6.7)	26 (14.4)	0.19
Active	16 (35.6)	57 (31.7)	0.31
Never	26 (57.8)	97 (53.9)	Ref
Tobacco use			
Prior	1 (2.2)	9 (5.0)	0.51
Active	10 (22.2)	56 (31.1)	0.99
Never	34 (75.6)	115 (63.9)	Ref

(continued)

Table 1. Continued.

Variables	Cases $n = 45$	Controls $n = 180$	p-Value[a]
Substance use			
Prior	1 (2.2)	10 (5.6)	0.39
Active	5 (11.1)	19 (10.6)	0.52
Never	39 (86.7)	151 (83.9)	Ref
Alcohol use			
Prior	3 (6.7)	9 (5.0)	0.75
Active	4 (8.9)	14 (7.8)	0.98
Never	38 (84.4)	157 (87.2)	Ref
Sexual risk factors[h]			
MSM	22 (18.8)	95 (81.2)	0.44
WSM	11 (18.6)	48 (81.4)	0.52
MSW	10 (25.0)	30 (75.0)	Ref

Median (IQR) or *n* (%) shown.
[a]*p*-Values are from univariate conditional logistic regression.
[b]ART = Anti-Retroviral Therapy.
[c]II: integrase inhibitor; EI: entry inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; the ART categories are not mutually exclusive.
[d,e]VL and CD4 values are closest/prior to VTE diagnosis.
[f]Detectable VL = >50copies/ml of blood.
[g]Medical history is on/prior to the date of VTE diagnosis.
[h]Men who have sex with men; women who have sex with men; men who have sex with women.
Missing values: VL = 36, CD4 = 19, and sexual risk factors = 9.

Table 2. Multivariate Conditional Logistic Regression Model for predictors of venous thromboembolism (VTE) among 225 patients receiving HIV primary care at the UAB 1917 Clinic as of December 31, 2011.

Variables	OR[a]	95% CI[b]	p-Value[c]
Age,[d] years	1.21	0.72; 2.04	0.467
Men	1.07	0.35; 3.24	0.910
White	2.30	0.78; 6.74	0.130
CD4 < 200, cells/μl of blood	4.50	1.52;13.37	0.007
HIV duration, years	0.87	0.78; 0.98	0.019
Log_{10} viral load, copies/μl of blood	1.33	0.90; 1.97	0.156
Surgical procedures	13.20	1.56; 111.41	0.018

[a]Odds ratio.
[b]Confidence interval.
[c]*p*-Values are from multivariate conditional logistic regression unless otherwise indicated.
[d]Age – OR represents the effect of 10-year change.

managed patients compared to PCP managed patients (1.69 vs.1.05; $p = 0.084$).

Discussion

Several studies have sought to determine risk factors associated with VTE among HIV positive populations but are hampered by several limitations including small sample sizes or inappropriately described control groups.[8,9,13,15] Information on the role of factors such as gender, and the classes and combinations of ART utilized in therapy remain controversial.[15,22] In the present study, we were able to control for these risk factors and found CD4 <200 cells/μl and prior surgical procedures were independent predictors for VTE. In addition, this is the first study to evaluate WAC outcomes using proportion of TTR among pharmacy-managed ACC and PCP-managed patients in an HIV care setting. The TTR among ACC managed patients was about 15% higher compared to those managed by PCPs. In our limited sample size, we were unable to show statistical significance, but our trend suggests the benefits of pharmacist managed WAC seen in general care settings extend to PLWHA, an important fact to consider as we prepare for caring for our aging HIV-infected patients.[23,26–30]

We observed an association of lower CD4 counts and increased VTE risk. This was the strongest predictor in the multivariable analysis. Advanced HIV disease may result in immune activation, triggering abnormal coagulant pathways and raising the risk of thrombosis.[9,11,38] VTE occurrence has been associated with lower CD4 values in other studies.[1,2,8,9,14,16,38] However, not all research is consistent with these

Table 3. Anticoagulation outcomes among 1917 Anticoagulation Clinic and UAB 1917 HIV primary care clinic managed patients ($n = 17$) as of December 31, 2011.

Variables	ACC managed patients ($n = 12$)	PCP managed patients ($n = 5$)	p-Value[a]
Patient related			
Age, years	46 (35–52)	42 (41–49)	1.000
Gender, *n* (%)			0.261[a]
Men	8 (67)	5 (100)	
Women	4 (33)	0 (0)	
Depression, *n* (%)	7 (58.3)	2 (40)	0.620[1]
Malignancy, *n* (%)	2 (16.7)	3 (60)	0.117[1]
Active tobacco use	4 (33.3)	1 (20)	1.000[1]
Active substance use	3 (25)	0 (0)	0.515[1]
Active alcohol use	3 (25)	1 (20)	1.000[1]
PI	5 (41.7)	3 (60)	0.620[1]
NNRTI	4 (33)	1 (20)	1.000[1]
NRTI	9 (75)	4 (80)	1.000[1]
INR related[c]			
Duration of therapy, days	138.5 (57–447)	203.0 (164–239)	0.642
Average INR gap, days[d]	16.3 (8.64–21.29)	17.0 (11.64–23.50)	0.570
Time within Therapeutic INR (TTR)[e]	0.562 (0.35–0.69)	0.305 (0.30–0.45)	0.174
Warfarin dose adjustments per patient month	1.69 (1.39–2.42)	1.05 (1.00–1.35)	0.084

Note: Median (IQR) shown unless otherwise indicated.
ACC: anticoagulation clinic; PCP: primary care providers; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor.
[a]*p*-Values are from Wilcoxon Rank-Sum tests unless otherwise indicated.
[b]Fisher's exact test.
[c]International normalized ratio.
[d]Mean gap between INR values per patient.
[e]Proportion of time INR within therapeutic range.

findings, and some have reported similar VTE occurrence at CD4 counts greater and less than 200 cells/μl.[11] Thrombosis in HIV is multifactorial[2] and much remains to be explained, but our results and much of the extant literature support a higher risk for VTE in individuals with low CD4 cell counts.

Prior surgical procedures was found to be a predictor of VTE among HIV-infected patients. Post-surgical immobilization or decreased mobility is associated with an increased risk of thromboembolic disease.[16] Our results are consistent with previous studies among the general population where patients hospitalized with previous surgery had as high as a 22-fold increased risk of VTE.[40] Future studies with larger sample sizes including multisite HIV cohorts will help further clarify if this risk is comparable or greater than that of the post-operative general population and can help discern the risk associated with different types of procedures; knowledge which will allow us to target those PLWHA at higher risk for aggressive VTE prevention.

The median duration of HIV at the time of thrombosis was 6.9 years in cases compared to 9.5 years in controls. For every one year increase in HIV duration, the odds of VTE decreased by 13% (0.87; CI = 0.78; 0.98; $p = 0.019$). We initially hypothesized that patients with longer duration of HIV were at risk for more prolonged HIV-related inflammation and thus were likely to be at higher thrombotic risk. Our results did not support this observation. The results may be influenced by many factors such as survivor bias as those with undiagnosed VTE may not have survived their initial episodes. Future analyses, perhaps including confirmation of cause of death beyond that available in public databases will be needed to further clarify the relationship of time of HIV diagnosis to VTE risk. In addition, we examined the association of prior use and type of ART with VTE and found no significant differences among cases and controls (Table 1). The relationship of ART and VTE continues to be controversial and needs further study with larger patient populations.[2,9,41,42]

Our study suggests improved anticoagulation control among pharmacist managed ACC patients (56.2% TTR) compared to those patients managed by their HIV PCPs (30.5% TTR). The results are similar to prior studies among general population which demonstrated a 40–90% TTR among ACC patients.[23,26,28,43] Pharmacists in the ACC setting are trained and follow standardized protocols for warfarin management. In contrast, there may be much individual variation among primary care providers. ACC patients are extensively educated on warfarin compliance, the importance of coming to visits and regular INR checks, and receive reinforcement of these concepts in subsequent visits. We found our median warfarin dose adjustments per patient month to be higher among ACC managed patients, suggesting closer follow-up and more frequent therapeutic dose adjustments. In an ACC, patients are seen frequently and pharmacists are able to respond quickly to changes in other medications, diet and other health conditions. We posit that while our results did not achieve statistical significance due to our modest sample size, the therapeutic trends observed for this approach support its use in HIV treatment settings. We found that a pharmacist-led ACC was feasible within the HIV outpatient care setting with minimal additional training and logistical support for our pharmacists. As PLWHA continue to age successfully and accrue additional risk factors for VTE, HIV care PCPs must look for ways to bring the advantages of a protocol driven ACC strategy to our patients, expanding our ability to provide comprehensive care.

Limitations

Our results may not be applicable to other patient populations, clinical settings or regions as this is a single cohort at an academic clinic in the southeast USA with a modest study sample size. Radiologic confirmations were not consistently available for all patients (e.g. transfer from outside facility, etc.) and hence were not specifically looked for to confirm VTE. Evaluation of some known risk factors such as BMI, pregnancy, prolonged hospitalization, history of trauma, duration and specific regimens of ART, genetic factors and family history of thrombosis was not possible due to variances in provider documentation and practice. Time from surgical procedure to VTE and classification of high and low risk surgical procedures were not possible as ''type of procedure'' was not consistently recorded among participants. However, had we been able to exclude low risk surgical procedures, the association found would most likely have been stronger than what was observed. Again owing to modest sample size, a separate analysis for PE and DVT patients was not possible. Our study sample for WAC outcomes was small as stringent inclusion criteria were applied to accurately evaluate TTR using the Rosendaal method. While dosing data were not consistently recorded for the PCP managed patients, we were not able to compare complication rates between anticoagulation strategies. Since per protocol, noncompliant ACC patients were discharged back to their referring PCPs for WAC management, a potential bias was created. In this study, only two ACC-managed participants were discharged back to their PCPs during our study period who eventually were loss to follow up from the 1917 Clinic shortly thereafter, hence, minimal PCP WAC care data for non-compliant participants were included in the analyses. Though TTR is a valid method for WAC, but as discussed in prior literature, it does not account for short-term risks with extreme INR values and no warfarin periods.[44] TTR is also sensitive to duration of warfarin therapy and patient factors.[44] Finally, as an observational study, we were able to describe associations but cannot attribute causation.

Strengths

This study contributes to the extant literature by exploring the associations between HIV and VTE including rarely controlled for risk factors in the existing literature. Other strengths of our analyses are the nested case control design and the use of well-established methodology in the UAB 1917 Clinic cohort with assiduous confirmation of VTE diagnoses by medical chart review.

Conclusions

In summary, we found CD4 count <200 cells/μl and prior surgical procedures to be predictors for VTE among our HIV-infected population. As the PLWHA population ages, VTE risk factors become more common and it is important for HIV care providers to be aware of risk factors for VTE. We discussed the early results and successful implementation of a protocol-driven, pharmacist-managed ACC treatment strategy incorporated within an HIV care setting providing descriptive data suggesting improved TTR among ACC-managed patients. The results of the study should be interpreted with caution owing to small sample size. Pharmacist-managed ACC is a viable strategy to provide optimal WAC to the increasing number of PLWHA that will face VTE and represents an important opportunity to benefit our patients.

Acknowledgements

Our study team would like to thank Research and Informatics Center (RISC) at UAB and the UAB 1917

Clinic personnel for their help with this project. Special thanks to Ashutosh Ranjan, MS for assistance with SAS 9.3 software; Suneetha Thogaripally and Anuj Kapil for data retrieval, and to Michael Mugavero, MD, MSc, Michael Saag, MD, MSc, Amanda Willig, PhD, and the UAB 1917 Clinic Cohort faculty and staff for their assistance with this project.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

JHW has received research support from the Bristol-Myers Squibb Virology Fellows Research Program for the 2006–2008 academic years, Pfizer, Tibotec Therapeutics, and Definicare, and has consulted for Bristol-Myers Squibb and Gilead Sciences. AOW has received research support from Definicare. GAB has received research support from the Bristol-Myers Squibb Virology Fellows Research Training Program for the academic years 2010–2012.

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