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CHALLENGES IN MANAGEMENT OF WARFARIN ANTI-COAGULATION IN ADVANCED HIV / AIDS PATIENTS WITH VENOUS THROMBOTIC EVENTS – A CASE SERIES FROM A RESEARCH CLINIC IN RURAL KERICHO, KENYA
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ABSTRACT

***Background*: Venous thrombotic events (VTE) occur at high rates in HIV/AIDS patients and are likely under-diagnosed in rural sub-Saharan Africa.**
***Objective*: To describe clinical presentations and challenges in the management of VTE in patients with advanced HIV/AIDS.**
***Design*: Case series from patients enrolled in a prospective observational cohort study.**
***Settings*: A clinical research centre in rural Kericho, Kenya.**
***Subjects*: Two hundred patients with median age 38 (30-47) years, BMI 16.9 (12.4-20.3) kg/m2, haemoglobin 9.3 (6.8-13.4) g/dL, CD4+ T-cell count 27 (4-77) cells/mm^3 and plasma HIV RNA 5.23 (3.70-5.88) log10copies/mL.**
***Interventions*: VTE cases were diagnosed by clinical presentation and Doppler/ radiographic confirmation. Anti-coagulation therapy was managed by a multidisciplinary team; patients were initiated on enoxaparin or heparin followed by warfarin.**
***Results*: Over two years, 11 patients (5.5%) experienced VTE. All but one (10/11, 90.9%) case occurred within six months of starting ART. Nine patients had peripheral VTE (five popliteal, four femoral) and two had cerebral sinus thromboses. VTE was diagnosed 52 (1-469) days after ART initiation, and 81.8% of cases were outpatients at presentation. All patients received at least one concomitant medication that could significantly interact with warfarin (efavirenz, nevirapine, lopinavir/ritonavir, rifampicin, trimethoprim-sulfamethoxazole, and fluconazole). A median of 39 (10-180) days and eight (4-22) additional clinic visits were required to achieve/maintain a therapeutic INR of 2-3. Two minor bleeding complications occurred. No recurrent VTE cases were observed.**
***Conclusion*: Consideration of VTE and preparedness for management in patients with advanced HIV/AIDS starting ART is critical in sub-Saharan Africa. Overcoming challenges in anti-coagulation is possible in rural settings using a multidisciplinary team approach.**

INTRODUCTION

Venous thrombotic events (VTE), most commonly deep venous thrombosis (DVT) and pulmonary embolism (PE) but to a lesser extent cerebral sinus thromboses, occur at higher rates in HIV / AIDS patients than in the general population (1-3). A hyper-coagulable state in advanced HIV / AIDS patients has been postulated as a risk factor for VTE (4). Studies have associated the hyper-coagulable state in these patients with abnormalities in the coagulation cascade. These include the presence of lupus anti-coagulant and anticardiolipin antibodies; increased levels of von Willebrand factor, fibrinogen,

and d-dimer; and, deficiencies of protein C, protein S, antithrombin III and heparin co-factor II (4, 5, 6). These abnormalities correlate with the severity of HIV-associated immunodeficiency (4). In rural sub-Saharan Africa, a region with the highest burden of HIV/AIDS, VTE is likely under diagnosed due to a low index of suspicion and lack of diagnostic tools (e.g. ultrasonography, computerised tomography (CT), and magnetic resonance imaging (MRI]). Untreated VTE may be an underappreciated factor leading to early morbidity and mortality in advanced HIV/AIDS patients in sub-Saharan Africa.

Oral anti-coagulation therapy with warfarin is the mainstay of VTE management (7). Safe and effective warfarin use is challenging due to its narrow therapeutic index, numerous medication and food interactions, and need for frequent laboratory monitoring (8-10). The challenge is further magnified in patients with advanced HIV/AIDS and VTE who require complex pharmacotherapy including ART and comorbid opportunistic infections prophylaxis and treatment (11). Warfarin drug interactions are well described with ART and HIV/AIDS-related medications including non-nucleosides reverse transcriptase inhibitors (NNRTI), (12-14) protease inhibitors (PI), (14-16) rifampicin, (17) and antimicrobial agents such as cotrimoxazole, (10,18) presenting numerous challenges in safely achieving and maintaining the desired international normalised ratio (INR) of 2-3.

Healthcare workers including doctors, clinical officers, nurses, and pharmacists in rural sub-Saharan Africa may have inadequate radiographic and laboratory resources and clinical experience to diagnose VTE and optimally manage anti-coagulation therapy. We present a case series of 11 patients with advanced HIV/AIDS who started ART and subsequently experienced VTE with emphasis on challenges and lessons learned in achieving and maintaining therapeutic warfarin anti-coagulation.

MATERIALS AND METHODS

The patients described in this case series were enrolled in the Immune Reconstitution Inflammatory Syndrome (IRIS) study (19). Conducted between February 2009 and April 2012, the IRIS study was a two year, prospective observational cohort study of ART-naive HIV-positive patients with CD4+ T cell count $<100/mm^3$ who initiated Kenya Ministry of Health (MoH) recommended ART. Kenya MoH first line ART consists of one non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse or transcriptase inhibitors (NRTI) (20,21). Opportunistic infections and other illnesses were managed according to the local standard of care (22). Hospitalised patients who were immobile or had additional risk factors for VTE were prescribed subcutaneous enoxaparin or heparin. The study was approved by the Kenya Medical Research Institute (KEMRI), US Uniformed Services University Infectious Disease (USU ID), and the US National Institute of Allergy and Infectious Diseases (NIAID) Institutional Review Boards. All patients provided written informed consent.

The KEMRI/Walter Reed Project (WRP) Clinical Research Centre (CRC) is located on the grounds of Kericho District Hospital; a MoH facility providing care to a rural, largely uninsured population (23). Kericho is located among the tea fields and plantations of Kenya's southern Rift Valley Province 260 kilometres northwest of Nairobi. The KEMRI/WRP CRC conducts HIV-1 vaccine, therapeutics, and health economics research as part of the US Military HIV Research Programme (MHRP) and includes a College of American Pathologists (CAP) accredited lab (24,25). The MoH in collaboration with KEMRI/WRP supports HIV care, prevention, and treatment services largely under the President's Emergency Plan for AIDS Relief (PEPFAR) program in Kericho and throughout the southern Rift Valley Province of Kenya (population of approximately 2.5 million) (26). Patients presenting with signs and symptoms consistent with VTE had confirmatory testing by Doppler ultrasonography and CT and/or MRI scans as indicated (7). A multidisciplinary approach was adapted for management of anti-coagulation therapy. Physicians and pharmacists provided staff education on warfarin dosing, monitoring and dosage modification, assessment of drug-drug interactions, and patient counselling. Nurses, clinical officers and a nutritionist who is also a social worker participated in the comprehensive care of patients. A dedicated pharmacist identified potential drug-drug interactions, provided patient counselling on warfarin use, and monitored patients' medication and dietary history. The multidisciplinary team reviewed and implemented appropriate dosing adjustments based upon clinical and laboratory data.

Following VTE diagnosis, those seen in the outpatient clinic were hospitalised. Subcutaneous enoxaparin or heparin was started followed by oral warfarin (Marevan®, Goldshield Pharmaceuticals, UK). INR values were checked at baseline and 1-3 day intervals until a therapeutic INR (2-3) was achieved, (27) when enoxaparin was stopped. If clinically appropriate, patients were discharged. INR was then monitored every five days. Once a stable therapeutic INR (two consecutive values of 2-3) was obtained, patients were monitored monthly or as clinically indicated. Warfarin dose adjustments were made in 1-2.5 mg increments based upon INR results. For an INR >5, warfarin was held until the INR returned to the therapeutic range. Additional monitoring and dosage adjustments occurred as indicated and based upon clinical scenarios (e.g. epistaxis, initiation of Mycobacterium tuberculosis (Tb) therapy).

De-identified data for this case series were extracted from study case report forms and complied on MS Excel worksheets. Simple statistics (n, [%] or median [range]) were used in describing characteristics of the case series.

RESULTS

Among 200 patients enrolled in the IRIS study and started ART, 11 (5.5%) cases of VTE were diagnosed (Table 1). All but one (10/11, 90.9%) VTE case occurred within six months of starting ART. Overall, patients comprising the case series were predominantly female (63.4%) aged 38 years (30-47) with median CD4+ T-cell count of 27 (4-77) cells/mm^3. Ten patients were receiving first line ART consisting of zidovudine or stavudine with lamivudine, plus efavirenz or nevirapine. One patient was receiving second line ART (zidovudine, lamivudine, and lopinavir/ritonavir) at the time of VTE diagnosis. Five patients had comorbid pulmonary Tb, and two had central nervous system (CNS) infections with altered mental status (one with cryptococcal meningitis and cerebral toxoplasmosis, the other patient with progressive multifocal leucoencephalopathy [PML]). Overall, the patients were underweight or malnourished (median body mass index 16.9 (range 12.4-20.3) kg/m^2), had hypoproteinemia (median albumin 2.8 (range 2.0-3.7) g/dL), and had signs of inflammation (median erythrocyte sedimentation rate 73 (range 10-132) mm/h).

Table 1
Baseline (pre-art) characteristics for patients with venous thrombotic events

Case	Age (yr)	Sex	CD4 (cells/mm^3)	HIV RNA (log_{10}copies/mL)	BMI (kg/m^2)	Albumin (g/dL)	Hgb (g/dL)	ESR (mm/h)	ART	Opportunistic Infections
1	30	M	9	5.78	15.8	3.67	10	115	EFV/d4T/3TC	Cryptococcal meningitis, toxoplasmosis, pulmonary Tb
2	47	F	4	5.23	18.7	2.64	8	110	EFV/d4T/3TC	Pulmonary Tb
3	38	F	60	3.70	18.5	3.63	12.9	10	EFV/ZDV/3TC	None
4	39	F	77	5.37	16.8	2.01	9.9	104	EFV/d4T/3TC	Pulmonary Tb
5	31	M	27	5.88	16.1	2.40	9.1	73	EFV/d4T/3TC	Pulmonary Tb
6	40	F	56	4.98	16.9	2.78	7.3	132	NVP/d4T/3TC	Genital herpes
7	38	F	32	5.73	13.7	2.15	6.8	58	EFV/d4T/3TC	Pulmonary Tb
8	36	F	15	5.58	17.8	3.26	9	84	EFV/d4T/3TC	Bacterial pneumonia
9	35	F	30	4.92	12.4	2.20	10	65	EFV/d4T/3TC	Oral candidiasis
10	42	M	7	4.89	16.9	3.63	9	15	LPV/r/ZDV/3TC	Progressive multifocal leucoence-phalopathy
11	37	M	13	5.08	20.3	3.74	13.4	13	NVP/ZDV/3TC	Genital herpes
Range	30-47	4-77	3.70-5.88	12.4-20.3	2.01-3.74	6.8-13.4	10-132			
Median	38	27	5.23	16.9	2.78	9.3	73			

ART = antiretroviral therapy, 3TC = lamivudine, d4T = stavudine, EFV = efavirenz, LPV/r = lopinavir/ritonavir, NVP = nevirapine, ZDV = zidovudine
BMI = body mass index, ESR = erythrocyte sedimentation rate, F = female, M = male, Hgb = haemoglobin, Tb = tuberculosis

VTE diagnoses were made a median of 52 (1-469) days after ART initiation. All but one VTE occurred in the first six months (Table 2). Nine (81.8%) VTE diagnoses were made at the outpatient setting, three of whom had previous hospitalisations with discharge dates four to 42 days before VTE diagnoses. Two patients had cerebral sinus thrombosis: one with transverse sinus thrombosis and the other with both carvernous and transverse sinus thromboses. Both patients presented with neurologic symptoms (psychosis, seizure, and headache) that prompted CNS imaging. One patient had a concurrent AIDS-associated CNS infection (PML). Peripheral VTE was diagnosed in nine patients, five patients with popliteal VTE and four with femoral VTE.

Table 2
Description of venous thrombotic events (vte) for individual patients

Case	VTE location	Symptoms at Presentation	outpt	Days since hospital discharge	ART	Days on ART before VTE	Latest CD4 (cells/mm^3) before VTE	Latest HIV RNA (copies/mL) before VTE
1	Popliteal DVT (left)	Left lower leg swelling x 4 days	Yes	42	EFV/d4T/3TC	136	117	<400
2	Popliteal DVT (left)	Left leg swelling, pain & warmth x 5 days	Yes	32	EFV/d4T/3TC	69	41	<400
3	Popliteal DVT (right)	Right calf swelling & pain x 1 wk, worse with walking	Yes	Never admitted	EFV/ZDV/3TC	469	94	<400
4	Popliteal DVT (right)	Severe right leg pain	Yes	Never admitted	EFV/d4T/3TC	52	197	<400
5	Popliteal DVT (left)	Left leg swelling & pain	Yes	Never admitted	EFV/d4T/3TC	18	82	2,151
6	Femoral DVT (left)	Painful left leg & thigh, fever x 6 days	No	Not applicable	NVP/d4T/3TC	126	128	<400
7	Femoral DVT (right)	Right leg swelling, tenderness, pain in walking x 4 days	Yes	4	EFV/d4T/3TC	46	34	<400
8	Femoral DVT (left)	Left leg swelling x 21 days	Yes	Never admitted	EFV/d4T/3TC	56	149	1,414
9	Femoral DVT (left) + PE	Left leg pain & swelling, difficulty walking x 4 days	Yes	Never admitted	EFV/d4T/3TC	1	No f/u*	No f/u*
10	Transverse sinus	Psychosis, patient also had PML	No	Not applicable	LPV/r/ZDV/3TC	36	39	<400
11	Cavernous sinus, right transverse sinus	Headache, seizure	Yes	Never admitted	NVP/ZDV/3TC	4	No f/u*	No f/u*
Median					52	82		
Range					1 - 469	13-197		

DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thrombotic event
ART = antiretroviral therapy, 3TC = lamivudine, d4T = stavudine, EFV = efavirenz, LPV/r = lopinavir/ritonavir, NVP = nevirapine, ZDV = zidovudine
Dx = diagnosis, Outpt = outpatient, f/u = follow-up
* No f/u = no follow-up CD4 or HIV RNA since pre-ART evaluation; both patients died (see text for further discussion)

Two patients died. One patient with PML died four months after VTE due to complications of PML. Another patient with femoral VTE died seven days after admission. This patient was hospitalised with left leg swelling and difficulty in walking. She was cachechtic, had oral candidiasis and was treated for probable cellulitis before femoral VTE was diagnosed and managed. Pulmonary embolism (PE) was found at autopsy and was considered the cause of death. The remaining nine patients completed warfarin

therapy with a treatment duration between six and ten months.

Warfarin dosing, INR values, drug interactions, and other clinical considerations warrant attention (Table 3). Warfarin drug-drug interactions were frequent. In addition to ART, all patients received either trimethoprim-sulfamethoxazole (enhanced warfarin effect) or dapsone for prophylaxis of opportunistic infections (OI) (e.g. Pneumocystis jirovecii, malaria, and diarrheal infections [for trimethoprim-sulfamethoxazole only]) and multivitamin. A notable number of patients (n=7) also received additional medications with potential drug interactions including rifampicin-based Tb treatment (n=5) (diminished warfarin effect) and fluconazole prophylaxis (n=1) (enhanced warfarin effect) for cryptococcal meningitis.

Table 3

Warfarin anti-coagulation, drug interactions, and clinic visits

Case	Initial Warfarin Dose (mg)	Concomitant Interacting Medications	Impact of Drug Interaction Upon Warfarin	Final Warfarin Dose (mg)	Days Until First Therapeutic INR (n)	Days Until Stable Therapeutic INR (n)1	% of Visits With Therapeutic INR2
1	5	EFV	↑	5	12	30	25
		RFP	↓				
		T-S	↑				
		FLU	↑				
2	7.5	EFV	↑	7.5	13	12	58.3
		RFP	↓				
		T-S	↑				
3	5	EFV	↑	7.5	6	10	66.7
		T-S	↑				
4	5	EFV	↑	7.5	10	60	37.5
		RFP	↓				
		T-S	↑				
5	7.5	EFV	↑	2.5	7	60	22.2
		RFP	↓				
		T-S	↑				
6	5	NVP	↓	10	16	50	47.3
		Doxy	↑				
7	5	EFV	↑	7.5	11	10	40
		RFP	↓				
		T-S	↑				
8	5	EFV	↑	10	7	20	42.9
9	2.5	EFV	↑	2.5	6	n/a(death)	n/a(death)
		T-S	↑				
10	7.5	LPV/r	↓	10	48	48	11
		T-S	↑				
11	5	NVP	↓	12.5		180	9.4
		T-S	↑				
Median	5			7.5	10.5	39	38.75
Range	2.5-7.5			2.5-12.5	6-48	10-180	9.4-66.7

1. Stable therapeutic INR was defined as two consecutive INR of 2-3

2. Proportion of visits with INR of 2-3 while on warfarin (number of results with INR of 2-3 divided by total number of INR results multiplied by 100%)

INR=International Normalized Ratio, Doxy=doxycycline, EFV=efavirenz, FLU=fluconazole, LPV/r=lopinavir/

ritonavir, NVP=nevirapine, RFP=Rifampicin, T-S=trimethoprim-sulfamethoxazole,.
The median warfarin starting dose was 5.0 (2.5-7.5) mg, and the median final dose was 7.5 (2.5-12.5) mg. All patients required warfarin dose adjustments in order to achieve and maintain a therapeutic INR of 2-3. Of all the INR readings obtained during follow-up, 38.8% (9.4%-66.7%) fell within the therapeutic range of 2-3. Patients required eight (4-22) extra clinic visits for warfarin monitoring. Two patients reported transient bleeding complications: one with haematuria (warfarin dose 7.5 mg, INR=10); and, one with recurrent epistaxis (warfarin dose 5 mg with an INR=2.0 and 12.5 mg with an INR=1.1).

DISCUSSION

We found in our research clinic in rural Kericho Kenya a high proportion of VTE in patients with advanced HIV/AIDS, most notably during the first six months of ART. VTE management posed additional challenges and burden on the clinical research team caring for these ill patients. The majority of patients were ambulatory at presentation and without traditional risks factors for VTE such as stasis, trauma, or known hypercoagulability (e.g. malignancy), beyond HIV. All the patients' anti-coagulation management was complicated by drug-drug interactions with medications used for treatment of HIV or opportunistic infections. In our clinic, using a multidisciplinary team approach, competency in warfarin management quickly improved after the diagnosis of the first few cases of VTE. Since the clinic team also managed the hospitalized patients, attention to VTE prophylaxis with enoxaparin or heparin increased for at risk patients, which likely prevented subsequent in- and outpatient VTE.

In this patient population, achieving and/or maintaining a therapeutic INR of 2-3 was a challenge. Periods of sub- or supra-therapeutic anti-coagulation pose risks to patients. Fortunately, there were no recurrent VTE. Warfarin was well tolerated overall with transient, non-serious bleeding complications (epistaxis and haematuria) in two patients. Some ART and drugs used for treatment or prevention of OI significantly interfered with warfarin metabolism or biosynthesis of vitamin-K dependent coagulation factors (10, 28) making it difficult to predict the warfarin dose required to achieve therapeutic INR.

Some patients received multiple cytochrome P450 enzyme inducing and inhibiting medications (e.g. efavirenz, rifampicin, and fluconazole) concomitantly, making it even more challenging to anticipate the net inhibitory or induction outcome. Adherence to ART, OI medications, and warfarin posed further challenges in successfully achieving anti-coagulation. In addition, alterations in routine dietary consumption of vitamin-K rich food products in this patient population may also have contributed to the INR fluctuations. Rivaroxaban, an oral factor Xa inhibitor, non-coumarin anti-coagulant, which does not require INR monitoring, is being recommended for treatment and prevention of VTE in resource rich settings (29). However, being a CYP3A4 substrate with potential for interactions with drugs used for OI such as rifampicin, the optimal dosing in patients receiving other CYP3A4 inducers or inhibitors is not known. Moreover, the cost of such therapy is prohibitive in our setting and most likely in most of sub-Saharan Africa.

Comparing to similar analyses of HIV and VTE, our prevalence (5.5%) was slightly higher than two US-based cohorts (2.8% and 3.7%) (2,4). This is likely reflective of our cohort representing patients with more advanced HIV and notably lower CD4+ T-cell counts. A similarity in the three cohorts was the occurrence of VTE in a relatively young population, which is in contrast to traditional risk factor of VTE in the HIV uninfected, which is more likely seen in older adults. Finally, a recent publication from an academic tertiary referral hospital in Kenya (30) reported a slightly higher time in therapeutic range of INR than in our series (47.0% vs. 38.8%). However, only a quarter of the patients had HIV and with less advanced disease.

Strengths of our case series include our study was prospective with close clinical follow-up using a CAP accredited laboratory assuring quality results. Additionally in contrast to data generated from urban and/or academic settings, ours is rural in nature and representative of where the majority of HIV burden is found in Kenya and sub-Saharan Africa. Limitations inherent to case series with a relatively small number of events must be recognised. However, the clinical significance of even low prevalence events warrants attention. Finally, resources available at our CRC are likely not available throughout rural Kenya and sub-Saharan Africa. Therefore, the results may not be directly generalizeable to all settings, but education and increased awareness are broadly available.

In conclusion, VTE is likely an under recognised problem leading to early morbidity and mortality in advanced HIV/AIDS patients initiating ART in rural Kenya and sub-Saharan Africa. Managing warfarin therapy in these patients is labour intensive and adds to inherent challenges in managing patients with advanced HIV/AIDS. Consideration of VTE and preparedness for warfarin management in patients with advanced HIV/AIDS starting ART will be critical for optimizing outcomes. Overcoming challenges in VTE diagnosis and anti-coagulation management is possible in rural settings with a vigilant and educated

multidisciplinary team.

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