

## Direct oral anticoagulants for the management of venous thromboembolism in patients with HIV – a single centre experience

Human immunodeficiency virus (HIV) infection remains one of the biggest health burdens worldwide, affecting 36.9 million people (World Health Organisation, 2017). Venous thromboembolism (VTE) has a reported incidence of 0.19–7.63% in those with HIV, representing a 2–10 fold increase compared to the general population (Bibas *et al*, 2011; Rasmussen *et al*, 2011). The seminal studies of direct oral anticoagulants (DOACs) in VTE did not report outcomes specifically for patients with HIV, and those on potentially interacting antiretroviral therapy (ART) were excluded from studies of direct factor Xa (Fxa) inhibitors (Schulman *et al*, 2009; EINSTEIN Investigators, 2010; Agnelli *et al*, 2013; The HOKUSAI-VTE Investigators, 2013). Thus there is very little published regarding the use of DOACs in this population. Consequently, VTE in these patients continues to be predominantly managed with low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKA). The main limiting factor for the use of FXa inhibitors in this population is the potential interaction with the ART due to inhibition/induction of the cytochrome P450 3A4 leading to a respective increase or decrease in DOAC concentration (Egan *et al*, 2014). In contrast, dabigatran is predominantly renally excreted; however its prodrug dabigatran etexilate is a substrate for P-glycoprotein, which is inhibited by protease inhibitors (PI; Egan *et al*, 2014). Concurrent administration of PI and dabigatran results in a significant increase in dabigatran bioavailability. This effect can be minimised by dose spacing of dabigatran two hours prior to PI administration (Egan *et al*, 2014). Thus of the four licenced DOACs, dabigatran has the least interaction with ART.

A recent literature review of DOAC use for atrial fibrillation (AF) in HIV-infected patients identified two case reports of successful use of dabigatran and three case reports of patients receiving prophylactic rivaroxaban post orthopaedic surgery. Two patients had bleeding complications with concomitant administration of the PI and one developed DVT whilst also on nevirapine. The authors comment on their own successful experience of using dabigatran for AF in more than 20 patients on ART (West *et al*, 2017). To our knowledge, use of apixaban and edoxaban has not been reported in patients with HIV and there are no reports of the use of DOACs for the treatment of VTE in this patient population.

We report our experience with DOACs for VTE management in 12 patients with HIV at King's College Hospital. We

identified patients with HIV prescribed a DOAC from electronic patient records from January 2013 to April 2018. Individual patient consent was not sought and anonymised data is presented. Twenty patients were identified, of these the indication for anticoagulation was VTE management in 15, with the remainder requiring anticoagulation for AF. Three patients with VTE were not under regular follow up at our centre and were excluded. The mean patient age was 60.3 years (range 43–83) with males accounting for 58.3% ( $n = 7$ ). Mean body mass index (BMI) was 29.7 kg/m<sup>2</sup> (standard deviation 7,  $n = 11$ ). Most patients had well controlled HIV at VTE diagnosis with 77.8% having no detectable plasma HIV RNA (7/9; missing data,  $n = 3$ ). No patient fulfilled the criteria for acquired immune deficiency syndrome. 11/12 patients were receiving ART with all treatment regimens including a nucleoside analogue reverse transcriptase inhibitor. Only two patients were prescribed PI (see Table I for further details).

The majority of DOAC use (83.3%) was for acute VTE (3 PE, 4 proximal DVT, 1 distal DVT and 1 long saphenous vein thrombosis within 3 cm of the saphenofemoral junction), with three patients commenced on DOAC for secondary VTE prevention [2 switched from long term warfarin for previous recurrent VTE and 1 initiated apixaban for secondary VTE prevention following a portal vein thrombosis (PVT) diagnosed 2 years prior]. Three patients with acute VTE had been previously anticoagulated for VTE but were not on anticoagulation at the time of recurrence (two with warfarin and one with rivaroxaban). Only 1/9 acute VTE was associated with a provoking factor (immobilisation associated with a lower limb fracture). Other VTE risk factors included obesity (BMI > 30 kg/m<sup>2</sup>) in 44.4% ( $n = 4$ ), long haul flight (>4 h,  $n = 1$ ) and known Factor V Leiden heterozygosity ( $n = 2$ ). Two patients received 3 months anticoagulation only; one due to high bleeding risk secondary to cerebral amyloid angiopathy and the other treated for a provoked distal DVT. The recommended duration for the remaining patients was longterm with median duration of follow-up on DOAC of 14 months (range 3–47).

Dabigatran was prescribed for 6 (50%), rivaroxaban for 3 (25%), apixaban for 2 (16.7%) and edoxaban for one (8.3%) patient. Potential drug interactions between DOAC and ART were present in three patients; one patient on efavirenz prescribed rivaroxaban, and two patients on PIs (see

Table 1. Summary of bleeding and recurrent venous thrombosis events.

Patient	ART	Indication for DOAC	DOAC regimen	Event	Description	Time post initiation of DOAC (months)
1.	Efavirenz, Tenofovir, Emtricitabine	Recurrent VTE	Dabigatran 150 mg bd	B	Menorrhagia disclosed at routine anticoagulation follow-up. Known pre-existing fibroids. Decision to persevere with dabigatran rather than switch to LMWH/warfarin. After initial 3 months, reduced to once daily dabigatran on the first 2 days of menstruation	2
				VTE	Recurrent PE. Lost to follow up for 11 months. Represented with new PE and reported discontinuing dabigatran for 4 months as asymptomatic. Re-initiated on LMWH with continued attendance at anticoagulation clinics over the last 4 weeks	13.5
2.	<b>Darunavir, Ritonavir,</b> Emtricitabine, Tenofovir	Recurrent VTE	Dabigatran 150 mg bd	VTE	Recurrent PE. Lost to follow up for 6 months during which time he self discontinued dabigatran. Initially managed with LMWH then switched back to dabigatran with improved adherence. Continues to attend anticoagulation follow-up 12 months post this event	13.5
3.	Emtricitabine, Tenofovir, Efavirenz	Proximal DVT	Dabigatran 150 mg bd	-		
4.	Emtricitabine, Tenofovir, Nevirapine	Proximal DVT	Dabigatran 150 mg bd	-		
5.	<b>Ritonavir, Atazanavir,</b> Emtricitabine, Tenofovir	Recurrent VTE, switched from long term warfarin	Dabigatran 150 mg bd	-		
6.	Efavirenz, Emtricitabine, Tenofovir	PE	Dabigatran 150 mg bd	-		
7.	Emtricitabine, Tenofovir, Raltegravir	PE	Rivaroxaban 20 mg od	-		
8.	<b>Efavirenz,</b> Lamivudine, Abacavir	Recurrent VTE	Rivaroxaban 20 mg od	-		
9.	Nil	Recurrent VTE	Rivaroxaban 20 mg od	-		
10.	Emtricitabine, Tenofovir, Raltegravir	Recurrent PE, switched from long term LMWH	Apixaban 5 mg bd	VTE	Internal jugular venous thrombosis 1 week post IVC filter retrieval (placed for perioperative cover prior to hysterectomy). Apixaban held for 3 days peri-procedurally. Apixaban increased to 10 mg bd for 1 week and then 5 mg bd long term	14
				B	Haemoptysis associated with community acquired pneumonia requiring hospitalisation. Temporary switch to enoxaparin for 10 days and then switched to secondary prevention dose of apixaban 2.5 mg bd	17
11.	Tenofovir, Emtricitabine, Raltegravir	Secondary VTE prevention for previous portal vein thrombosis	Apixaban 2.5 mg bd	B	Asymptomatic iron deficient anaemia, presumed occult gastrointestinal loss. Apixaban withdrawn	6
12.	Nevarapine, Lamivudine, Abacavir	Distal DVT	Edoxaban 60 mg od	-		

ART, antiretroviral therapy; DOAC, direct oral anticoagulant; VTE, venous thromboembolism; B, bleeding; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; IVC, inferior vena cava; -, no event. ART with potential interaction with selected DOAC are highlighted in **bold**.

Table I for details) prescribed dabigatran (both were instructed to take dabigatran two hours prior to PIs). Both patients attended for dabigatran levels with adequate exposure demonstrated for one (trough level 48.5, expected range 39–95; Gosselin *et al*, 2018). The other had two undetectable levels and later admitted he was not taking dabigatran at the time of testing (see Table I, patient 2). The third patient on efavirenz and rivaroxaban was treated twice for acute VTE without early recurrence (the second event occurred 12 months following planned discontinuation of rivaroxaban). He remains on extended rivaroxaban 20mg daily without recurrence (37 months follow up). Efavirenz is an inducer of CYP3A4 and therefore has the potential to reduce rivaroxaban levels.

There were two bleeding events, and three recurrent VTEs (all associated with interruption of anticoagulation), involving three patients (refer to Table I for further details).

HIV infection is a recognised risk factor for VTE and is highly prevalent globally. With increasing use of DOACs due to their established efficacy, safety and greater convenience compared to conventional anticoagulation, there is a need for this therapy to be evaluated in the HIV population. Our experience in 12 patients has been promising and represents the largest published cohort of patients with HIV treated with a DOAC for VTE. However, the management is complex and we suggest such patients are managed in a specialist centre.

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## Author contributions

RO collected the data and wrote the first draft. RKP, CT, JC, RA, LNR were responsible for treatment of these patients, critically reviewed and approved the final manuscript. LNR conceived the idea for the manuscript and co-wrote the paper.

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## References

- Agnelli, G., Buller, H.R., Cohen, A., Curto, M., Gallus, A.S., Johnson, M., Porcari, A., Raskob, G.E. & Weitz, J.I. (2013) Oral apixaban for the treatment of acute venous thromboembolism. *New England Journal of Medicine*, **369**, 799–808.
- Bibas, M., Biava, G. & Antinori, A. (2011) HIV-associated venous thromboembolism. *Mediterranean Journal of Hematology and Infectious Diseases*, **12**, e2011030.
- Egan, G., Hughes, C.A. & Ackman, M.L. (2014) Drug interactions between antiplatelet or novel oral anticoagulant medications and antiretroviral medications. *Annals of Pharmacotherapy*, **48**, 734–740.
- EINSTEIN Investigators. (2010) Oral rivaroxaban for symptomatic venous thromboembolism. *New England Journal of Medicine*, **363**, 2499–2510.
- Gosselin, R.C., Adcock, D.M., Bates, S.M., Douxfils, J., Favaloro, E.J., Gouin-Thibault, I., Guillerme, C., Kawai, Y., Lindhoff-Last, E. & Kitchen, S. (2018) International Council for Standardisation in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. *Thrombosis & Haemostasis*, **118**, 437–450.
- Rasmussen, L.D., Dybdal, M., Gerstoft, J., Kronborg, G., Larsen, C.S., Pedersen, C., Pedersen, G., Jensen, J., Pedersen, L., Sørensen, H.T. & Obel, N. (2011) HIV and risk of venous thromboembolism: a Danish nationwide population-based cohort study. *HIV Medicine*, **12**, 202–210.
- Schulman, S., Kearon, C., Kakkar, A.K., Mismetti, P., Schellong, S., Eriksson, H., Baanstra, D., Schnee, J., Goldhaber, S.Z. & for the RE-COVER Study Group. (2009) Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *New England Journal of Medicine*, **361**, 2342–2352.
- The HOKUSAI-VTE Investigators. (2013) Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *New England Journal of Medicine*, **369**, 1406–1415.
- West, T.A., Perram, J. & Holloway, C.J. (2017) Use of direct oral anticoagulants for treatment of atrial fibrillation in patients with HIV: a review. *Current Opinion in HIV & AIDS*, **12**, 554–560.
- World Health Organisation. (2017) HIV/AIDS data and statistics. Available at: <https://www.who.int/hiv/data/en/>