Increasing Utilization of Direct Oral Anticoagulants (DOACs) and Drug Interactions in People Living with HIV (PLWH) on Antiretroviral Therapy (ART): Data from the DC Cohort

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Background

- With effective ART, PLWH are living longer and may develop age-related co-morbidities.
- The CHEST guidelines recommend DOACs as first-line agents over warfarin for deep vein thromboembolism and pulmonary embolism treatment due to less bleeding and less frequent monitoring. Both warfarin and DOACs are considered Class I recommendations for atrial fibrillation.
- Five DOACs have been FDA approved: dabigatran (2010), rivaroxaban (2011), apixaban (2012), edoxaban (2015), and betrixaban (2017).
- DOAC dosing is complex and varies dependent on several factors including age, indication for anticoagulation, body weight, and renal function.
- There are several additional challenges to widespread use of DOACs among PLWH receiving ART:
  - Significant drug interaction potential with strong CYP3A4 and p-glycoprotein inhibitors including ritonavir (RTV) and cobicistat (COBI)
  - Limited pharmacokinetic drug interaction data between DOACs and antiretrovirals
  - **Use of COBI or RTV with rivaroxaban is not recommended; with apixaban, dose reduction is needed. With COBI, dabigatran dose reduction or avoidance may be necessary depending on renal function.**
  - Unlike warfarin, there are no well-established surrogate markers for monitoring the efficacy and/or toxicity of DOACs.

Study Objective

- To characterize evolving trends in oral anticoagulant use and the prevalence of concomitant use of DOACs with ritonavir or cobicistat boosted ART among PLWH in the Washington DC area.

Methods

- The DC Cohort is a clinic-based, longitudinal observational cohort of PLWH established in 2011.
- The DC Cohort database was queried for participants who were prescribed oral anticoagulants (warfarin or DOACs)
- The analysis included participants from 11 outpatient sites from January 1, 2011 to March 31, 2017.
- Study assessments:
  - Each individual course of a medication was considered a unique event. Overlap between prescriptions for warfarin, DOACs, and RTV or COBI was assessed.
  - Data on bleeding events following the initiation of warfarin or a DOAC was collected. Individual bleeds were defined as new ICD-9 or ICD-10 codes, separated by at least 30 days.
- Data collection:
  - Age, race, sex, BMI, pertinent medical history, laboratory results (renal function, hepatic function, CD4 cell count, HIV-1 RNA), ICD-9 and ICD-10 diagnoses, anticoagulant prescriptions, duration of anticoagulant use, potential indication for anticoagulation, concomitant medications, and bleeding events.
- Descriptive statistics of individuals prescribed DOACs and warfarin were generated. Yearly trend in oral anticoagulant prescriptions was assessed.

Results

- Among 8,315 PLWH enrolled during the study period, there were **239** anticoagulant prescriptions (96 DOAC, 143 warfarin) for 207 persons.
- Most common indications for anticoagulation included VTE (26%), PE (20%), and atrial fibrillation (11.7%). Indication was not documented in 43.1%.

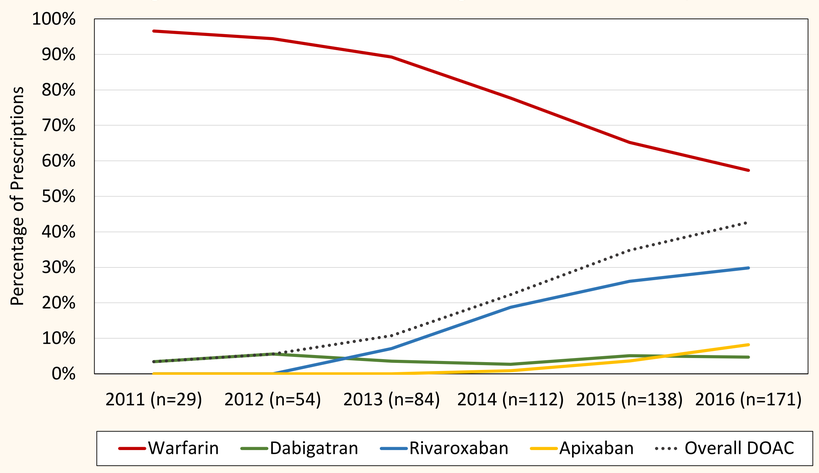
Table 1: Demographics and Baseline Characteristics

	Total DOAC (N=96)	Warfarin (N=143)	Total Overall (N=239)
Male (%)	84	80	82
Age at Anticoagulation Initiation (yrs, mean ± SD)	58 ±10.55	55 ±11.07	56 ±10.91
<30 years (%)	1.0	3.5	2.5
30-59 years (%)	52.1	62.3	58.1
60-69 years (%)	37.5	28.0	31.8
≥70 years (%)	9.4	6.3	7.5
Black, n (%)	75 (78.1)	120 (83.9)	195 (81.6)
White, n (%)	13 (13.5)	15 (10.5)	28 (11.7)
Hispanic, n (%)	2 (2.1)	3 (2.1)	5 (2.1)
Other/Unknown, n (%)	6 (6.2)	5 (3.5)	12 (4.6)
Weight, kg (mean ± SD)	84 ±21 (n=74)	90 ±29 (n=113)	87 ±26 (n=187)
BMI, kg/m², (mean ± SD)	27 ±6 (n=58)	30 ±10 (n=77)	28 ±8 (n=135)
Comorbidities, n (%)			
Hypertension	50 (52.1)	69 (48.3)	119 (49.8)
CKD	33 (34.4)	55 (38.5)	88 (36.8)
Diabetes	24 (25.0)	35 (24.5)	59 (24.7)
Malignancy	22 (22.9)	32 (22.4)	54 (22.6)
Anemia	15 (15.6)	30 (21)	51 (21.3)
Cardiac dysrhythmias	21 (21.9)	25 (17.5)	46 (19.2)
Hepatitis B	9 (9.4)	6 (4.2)	15 (6.3)
Hepatitis C	21 (21.9)	25 (17.5)	46 (19.2)
Hepatitis, other or unspecified	21 (21.9)	30 (21)	51 (21.3)
COPD/Bronchiectasis	20 (20.8)	20 (14)	40 (16.7)
Acute/Unspecified renal failure	9 (9.4)	24 (16.8)	33 (13.8)
Hepatic Impairment or Liver disease	13 (13.5)	19 (13.3)	32 (13.4)
Coronary atherosclerosis/ other heart disease	8 (8.3)	13 (9.1)	21 (8.8)

Table 2: HIV History

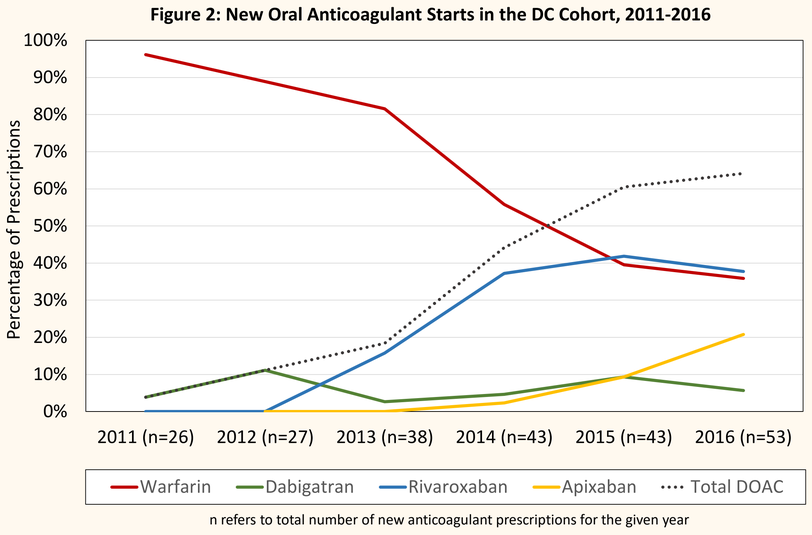
	Total DOAC (N=96)	Warfarin (N=143)	Total Overall (N=239)
Prescribed ART at time of anticoagulation initiation, n (%)	93 (97)	134 (94)	227 (95)
Yrs from HIV dx to anticoagulant initiation, mean +/- SD	16 ± 9	15 ± 8	15 ± 8
CD4 Nadir (cells/mm³), n (%)			
Nadir, mean (median) ±SD	241 (215)±181	213 (150)±201	224 (182)±193
<200	44 (46%)	85 (59%)	129 (54%)
200-500	41 (43%)	44 (31%)	85 (36%)
> 500	11 (11%)	14 (10%)	25 (10%)
Most recent CD4 prior to anticoagulant initiation (cells/mm³), n (%)			
<200	13 (14%)	15 (10%)	28 (10%)
200-500	30 (31%)	59 (41%)	89 (37%)
>500	42 (44%)	52 (36%)	94 (39%)
Unknown	11 (11%)	17 (12%)	28 (12%)
Most recent HIV-VL prior to anticoagulant initiation (c/ml), n (%)			
<200	72 (75%)	113 (79%)	185 (77%)
>200	12 (13%)	15 (10%)	27 (11%)
Unknown	12 (13%)	15 (10%)	27 (11%)

Figure 1: Trends in Overall Oral Anticoagulant Use in the DC Cohort, 2011-2016



n refers to total number of patients on anticoagulation during the given year

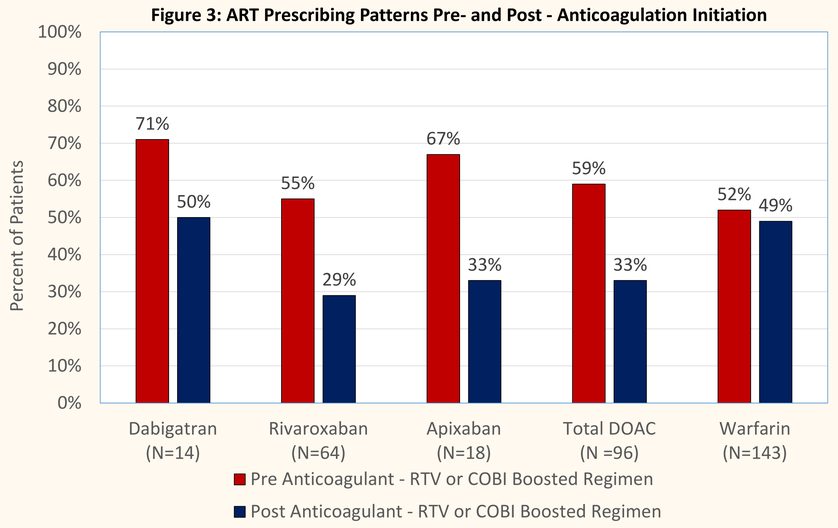
Figure 2: New Oral Anticoagulant Starts in the DC Cohort, 2011-2016



n refers to total number of new anticoagulant prescriptions for the given year

- DOACs accounted for 3% of total anticoagulant use in 2011, increasing to 43% in 2016 [Figure 1].
- DOACs accounted for 64% of all new anticoagulant prescriptions by 2016 [Figure 2].
- 25 patients switched from warfarin to a DOAC and 1 patient switched from a DOAC to warfarin.
- Rivaroxaban was the most frequently prescribed DOAC (70%) in 2016, followed by apixaban (19%), and dabigatran (11%).
- Apixaban was utilized more often in patients with CrCl < 30 ml/min and higher serum creatinine.

Figure 3: ART Prescribing Patterns Pre- and Post - Anticoagulation Initiation



Changes in ART prescribing were assessed at 1 month post anticoagulation initiation. These changes were consistent at 6 months post anticoagulation.

- Most commonly prescribed ARVs were raltegravir and darunavir based ART.
- Among PLWH on DOACs, 59% were on boosted ART prior to DOAC; 1 month after DOAC initiation, this decreased to 33%.
- **55% in the rivaroxaban group were receiving boosted ART prior to anticoagulant initiation. 29% still received boosted ART 1 month after rivaroxaban initiation.**

Table 3: Number of Reported Bleeding Events while on Boosted vs. Un-boosted ART

	RTV or COBI Boosted ART	Un-boosted ART	Total
On Warfarin	6	11	17
On DOAC	2	2	4
Total Patients	8	13	21

- 8.9% of people on ART and receiving anticoagulation had a documented bleeding event, 4.2% of DOAC patients and 12% of warfarin patients.
- No significant differences in the number of patients who had documented bleeds between those on boosted vs. un-boosted ART (p = 0.6621).

Conclusions

- In this cohort, DOAC use increased significantly over time from 3% of all anticoagulant prescriptions in 2011 to 43% in 2016. Rivaroxaban was the most prescribed DOAC.
- Despite the recommendation to avoid co-administration with ritonavir or cobicistat boosted ART, concomitant use was documented in 29% of rivaroxaban recipients.
- Feedback should be provided to clinicians on DOAC utilization trends and potential ART drug interactions.
- Limitations of this analysis include:
  - Retrospective data collection with reliance on ICD 9 and 10 codes
  - DOAC dosing could not be fully evaluated (weight, renal function, other labs)
  - Apixaban and dabigatran prescriptions could not be assessed for dose adjustments when co-administered with RTV or COBI.
  - Bleeding events were not systematically collected.

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