Warfarin Therapy in the HIV Medical Home Model: Low Rates of Therapeutic Anticoagulation Despite Adherence and Differences in Dosing Based on Specific Antiretrovirals

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Abstract

To determine the indications for, rates of therapeutic anticoagulation during, and complications of warfarin therapy in HIV-infected individuals, in whom long-term anticoagulation is frequently indicated. To identify risk factors for nonoptimal anticoagulation and to determine if warfarin dosing is differentially affected by specific antiretroviral agents. Retrospective study of a dedicated anticoagulation program at one of the largest clinics for HIV-infected individuals in the United States. Seventy-three HIV-infected individuals on warfarin were followed for a total of 911 visits. The rate of therapeutic international normalized ratio (INR) levels was 34.5% when including only visits at which patients were assessed to be adherent with warfarin. In multivariable analysis, injection drug use at baseline was an independent risk factor for subtherapeutic INR (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.3–4.7, $p=0.01$). Additionally, warfarin adherence was protective of both subtherapeutic (OR 0.4, 95% CI 0.2–0.6, $p<0.0001$) and supratherapeutic (OR 0.5, 95% CI 0.3–0.9, $p=0.02$) INR status. Efavirenz-based antiretroviral regimens were associated with lower weekly warfarin doses (46 mg) to maintain therapeutic INR compared to lopinavir/ritonavir-based regimens (68 mg; $p=0.01$) and atazanavir/ritonavir-based regimens (71 mg; $p=0.007$). Consistently therapeutic warfarin therapy is difficult to achieve in HIV-infected individuals, even with a dedicated anticoagulation program. Adherence to warfarin therapy is important but rates of therapeutic INR levels are nonetheless low. Lower warfarin dosing was required for efavirenz compared to two commonly used protease inhibitor-based regimens. Because of these factors, the emergence of new oral anticoagulants is an important development for HIV-infected individuals who require long term anticoagulation therapy.

Introduction

MULTIPLE STUDIES have demonstrated that individuals with HIV infection are more likely to develop clinically significant thromboses at rates that are up to 10 times that of the HIV-uninfected population.^{1–3} The exact mechanism for this hypercoagulability is unknown, but may involve abnormal levels of antiphospholipid antibodies and anticoagulant proteins, monocyte overexpression of thromboplastin, concurrent malignancies, immobilization, and the administration of prothrombotic medications.^{4–6} Confusing matters is the fact that abnormal levels of free protein S and antiphospholipid antibodies are common in HIV-infected individuals and are

not necessarily associated with the development of thromboses.^{7,8} While low CD4⁺ T-cell count is a risk factor for thromboses, it is notable that not all prothrombotic markers are normalized with highly active antiretroviral therapy (HAART).^{9,10} Indeed, the receipt of HAART has not been found to be protective against thrombotic events.¹ Hence, HIV-infected individuals continue to be at elevated risk for these events and often require prolonged anticoagulation therapy.¹¹ Additionally, with the HIV-infected population living significantly longer in the HAART era,¹² individuals are at risk for other conditions that require prolonged anticoagulation such as cardiac arrhythmias and valvular heart disease.

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The most commonly recommended standard of care for individuals with deep thrombosis not associated with malignancy or other indication for prolonged anticoagulation in the United States is therapy with warfarin, an oral vitamin K antagonist.¹³ Due to warfarin's narrow therapeutic index and its significant potential for drug interactions, frequent monitoring and close follow-up are essential for individuals taking this agent.¹⁴ Warfarin is a racemic mixture of R and S enantiomers that are metabolized through different cytochrome P450 enzymes. Antiretroviral medications, particularly protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), have the potential to either induce or inhibit cytochrome P450 enzymes and thus affect the anticoagulation potency of warfarin.¹⁵ The clinical implications of these warfarin-antiretroviral interactions are limited to case reports.^{16–18} In addition, the long-term use of warfarin in the setting of HIV and HAART has not been formally described. Given that there are over 1 million HIV-infected individuals in the United States and over 30 million HIV-infected individuals worldwide, an analysis of warfarin therapy in this population is of interest to the thousands of providers who work in this field.

The purpose of this study was to describe the long-term experience of a dedicated warfarin clinic for HIV-infected individuals as part of an overall medical home model, which has been advocated as a paradigm for the management of complex medical conditions such as HIV.¹⁹ We specifically sought to describe the demographic characteristics of HIV-infected individuals who require anticoagulation, rates of adherence to warfarin, rates of therapeutic anticoagulation, complications of anticoagulation, factors associated with nontherapeutic international normalized ratio (INR), rates of thrombosis recurrence, and the effect of commonly used antiretrovirals that influence P450 enzymes on warfarin dosing. We hypothesized that warfarin dosing to achieve therapeutic INR would be differentially affected by particular antiretrovirals, specifically ritonavir-boosted protease inhibitors versus efavirenz.

Methods

Clinic background and definitions

The Grady Health System Infectious Diseases Program (IDP) in Atlanta, Georgia is one of the largest centers for HIV care in the United States with an active census of over 4500 HIV-infected patients. The IDP has been designed to care for patients with advanced HIV infection, meaning that the majority of patients have either CD4⁺ T-cell count less than 200 cells per microliter or an AIDS-defining disease at enrollment. Pharmacy, mental health, and other services are also provided as part of a patient-centered medical home model.¹⁹ The IDP has two full-time infectious disease pharmacists who direct the management of patients on anticoagulation therapy. Anticoagulation clinic visits are in addition to patient visits with primary medical providers (physician or physician extender). The framework for this management comes from the American College of Chest Physicians (ACCP) guidelines for treatment of thrombosis and vitamin K antagonist therapy.^{13,20} It includes clinic visits at least once every 4 weeks in stable patients (more frequently if changes are needed) in which the pharmacist assesses warfarin adherence, asks about bleeding events, and monitors the blood INR to ensure therapeutic

anticoagulation. Changes in warfarin dosing and use of vitamin K were based on the ACCP guidelines, and warfarin dosing changes were made in increments of 10–20%. INR measurements were performed by the Grady Health System central coagulation laboratory using an FDA-approved commercial system. Point of care INR testing was not in place during the time of the study.

For this study, we reviewed all individuals who were followed for anticoagulation therapy at the IDP from 2004 (time of implementation of current electronic laboratory record) through 2009. Demographic parameters were established at baseline and laboratory and medications parameters were followed over time. Patients who were seen at the IDP for HIV care but were followed for anticoagulation by an outside warfarin clinic were not included in the study. Patients were categorized as adherent with warfarin at pharmacy clinic visits if the patient confirmed that the warfarin was taken as prescribed daily and the patient was able to accurately communicate the dosing regimen. If the patient received warfarin directly from the IDP (as opposed to an outside pharmacy), the IDP pharmacy system was also reviewed to ensure that warfarin was picked up once monthly. Adherence to other medications, including antiretrovirals, was not rigorously assessed at these pharmacy visits, but a list of all other active medications was reviewed verbally with each patient.

For this analysis, the diagnosis of thrombosis or other indication for anticoagulation required radiographic, echocardiographic, or electrocardiographic (if cardiac arrhythmia) confirmation to be included. Mental illness was defined by the diagnosis of depression, bipolar disorder, or schizophrenia at baseline. Other baseline characteristics included alcohol abuse, cocaine use, or injection drug use as documented by the patient's regular medical provider. Hospitalization was defined as inpatient admission for at least 2 days in the previous 4 weeks prior to anticoagulation initiation. Hepatitis B virus (HBV) infection was defined by surface antigen positivity at baseline with no documentation of clearance during follow-up. Hepatitis C virus (HCV) infection was defined by serum antibody positivity at baseline with either positive or unknown serum HCV RNA level and no history of HCV treatment prior to or during follow-up. Per U.S. guidelines, therapeutic INR for thromboembolic disease and cardiac arrhythmia was defined as 2.0–3.0 and therapeutic INR for mechanical heart valve replacement was defined as 2.5–3.5.^{13,21,22}

Statistical analysis description

Proportions were compared between the two anticoagulation groups (deep venous thrombosis [DVT]/pulmonary embolus [PE] versus others) using the χ^2 or Fisher's exact test. Continuous variables were compared between anticoagulation groups using the Wilcoxon rank-sum test or the *t* test. An extension of the generalized estimating equations (GEE) introduced by Liang and Zeger^{23,24} was used to analyze the correlated nominal INR outcome data (subtherapeutic, therapeutic, and supratherapeutic). These three INR multinomial categories were assumed to have no intrinsic ordering. The GEE methodology, using an exchangeable correlation structure with a polytomous logistic marginal distribution, was used to model INR status at each clinical visit and relate the INR status to set covariables (baseline: alcohol abuse, cocaine abuse, injection drug use, mental illness, hepatitis B or C

diagnosis, enrollment age; time dependent covariate: warfarin adherence was assessed at each clinical visit). Univariable and multivariable analyses of INR status were performed using these 7 risk factors. The odds ratio and its 95% confidence interval were calculated for each risk factor in the presence of others in the final model. The odds ratio was provided for subtherapeutic INR status relative to therapeutic INR status and for supratherapeutic status relative to therapeutic INR status in both the univariable and multivariable analyses. A standard GEE univariable analysis was performed for the repeated binary data within patient for viral load (≥ 100 copies per milliliter or < 100 copies per milliliter; exchangeable binomial-logit model) and a similar longitudinal GEE univariable analysis was performed for the warfarin adherence data. Longitudinal analyses of average weekly warfarin dose were performed for the subset of 31 patients on one of three PI/NNRTI-based regimens who were adherent at each clinic visit

and achieved therapeutic INR. The average weekly warfarin dose was analyzed with a means model using SAS Proc Mixed (version 9, SAS, Cary, NC) providing estimates of the mean by treatment group (lopinavir/ritonavir; efavirenz or atazanavir/ritonavir). A compound-symmetry form in the longitudinal measurements was assumed for the warfarin dose, and robust estimates of the standard errors of parameters were used to perform statistical tests and construct 95% confidence intervals. As an exploratory analysis, the model was then refitted and included trimethoprim-sulfamethoxazole (yes or no at each clinic visit) as an additional covariable.

Results

Demographics

A total of 73 patients were identified (see Table 1 for baseline demographics). The majority of patients were male

TABLE 1. BASELINE CHARACTERISTICS FOR 73 HIV-INFECTED PATIENTS STARTED ON WARFARIN THERAPY

	Overall (n=73)	DVT/PE (n=60)	Others (n=13)	p Value
Age (72 available)	43 $\pm$ 10 ^a	43 $\pm$ 10	44 $\pm$ 7 (n=12)	0.65 ^b
CD4 count (72 available)	57191 ₃₄₆ ^c	53195 ₃₅₆ (n=59)	95151 ₂₀₀	0.47 ^d
Log10 (HIV RNA) (70 available)	1.702.58 _{4.62}	1.702.40 _{4.62} (n=57)	1.953.00 _{4.15}	0.98 ^d
Gender: male	65 (89.0%)	53 (88.3%)	12 (92.3%)	1.00 ^e
Race/ethnicity:				
African American and African	61 (83.6%)	51 (85.0%)	10 (76.9%)	0.58 ^e
Latino	2 (2.7%)	2 (3.3%)	0 (0.0%)	
White	10 (13.7%)	7 (11.7%)	3 (23.1%)	
Initial indications for anticoagulation:				
Deep venous thrombosis	35 (47.9%)			
Pulmonary embolus	13 (17.8%)			
Atrial fibrillation	4 (5.5%)			
Heart valve replacement	1 (1.4%)			
Atrial flutter	1 (1.4%)			
Ischemic stroke	2 (2.8%)			
Pulmonary hypertension	1 (1.4%)			
Ventricular thrombus	2 (2.8%)			
Papillary fibroma	1 (1.4%)			
Myocardial infarction	1 (1.4%)			
Deep venous thrombosis and pulmonary embolus	10 (13.7%)			
Deep venous thrombosis and heart valve replacement	1 (1.4%)			
Deep venous thrombosis and pulmonary embolus and thrombotic stroke	1 (1.4%)			
Diagnosed as inpatient or outpatient				0.70 ^e
Inpatient	15 (20.5%)	12 (20.0%)	3 (23.1%)	
Outpatient	50 (68.5%)	42 (70.0%)	8 (61.5%)	
Unknown	8 (11.0%)	6 (10.0%)	2 (15.4%)	
Hospitalization	21 (28.8%)	20 (33.3%)	1 (7.7%)	0.09 ^e
Malignancy	8 (11.0%)	6 (10.0%)	2 (15.4%)	0.63 ^e
Active opportunistic infection	15 (20.5%)	15 (25.0%)	0 (0.0%)	0.06 ^e
Surgical procedure	17 (23.3%)	14 (23.3%)	3 (23.1%)	1.00 ^e
Hepatitis B/C	15 (20.6%)	13 (21.7%)	2 (15.4%)	1.00 ^e
Alcohol abuse	20 (27.4%)	18 (30.0%)	2 (15.4%)	0.49 ^e
Cocaine use	19 (26.0%)	16 (26.7%)	3 (23.1%)	1.00 ^e
Injection drug use	9 (12.3%)	7 (11.7%)	2 (15.4%)	0.66 ^e
Mental illness	21 (28.8%)	14 (23.3%)	7 (53.9%)	0.04 ^e

^aMean $\pm$ standard deviation.

^bt test.

^clower quartile median upper quartile.

^dWilcoxon rank sum test.

^eFisher's exact test.

DVT/PE, deep venous thrombosis; PE, pulmonary embolism; SD, standard deviation.

(89.0%) and either African American or African (83.6%). 60 of the 73 patients (82.2%) had either DVT, PE, or a combination of the two as the indication for anticoagulation. One third of these 60 patients were diagnosed during or immediately after a hospitalization. 15 of the 60 patients (25.0%) had at least one active opportunistic infection (OI) at the time of diagnosis. The most common OIs were *Pneumocystis carinii* pneumonia (8/60: 13.3%) and mucocutaneous candidiasis (5/60: 8.3%), followed by disseminated *Mycobacterium avium* infection, central nervous system toxoplasmosis, and cytomegalovirus retinitis (each 2/60: 3.3%). Six of 60 patients (10.0%) had a concurrent malignancy at the time of DVT or PE diagnosis (2 lymphoma, 2 squamous cell cancer of the anus, 1 Kaposi's sarcoma, and 1 lung cancer). Two patients had documented low protein S activity levels on the day of thrombosis diagnosis. At some point in their care, 8 other patients with thrombosis had documented low protein S activity levels and 3 patients had documented low protein C activity levels. However, these 11 patients were either on warfarin or had an unknown anticoagulation status when the level was drawn, making the results difficult to interpret. None of the patients with thrombosis had abnormal test results for antithrombin III deficiency, Factor V Leiden, antiphospholipid antibodies, or homocysteine, though the majority of patients were not checked for these.

Of the 60 patients, 34 (56.7%) were receiving prescriptions for HAART at the time of DVT/PE. Plasma HIV RNA levels were available for 33 of these 34 patients at baseline. The median level was 230 copies per milliliter (minimum < 50

copies per milliliter, maximum > 500,000 copies per milliliter). Of these 33 patients, 15 (45.5%) had plasma HIV RNA levels of < 100 copies per milliliter at the time of DVT/PE. In terms of age, gender, race/ethnicity, HBV/HCV status, CD4⁺ T-cell count, and HIV RNA level, patients with DVT/PE were not significantly different from patients with other indications for anticoagulation at baseline.

Anticoagulation clinic visits, adherence, and virologic control

As shown in Table 1, there were 15 patients (20.5% of total cohort) diagnosed with an indication for anticoagulation in the inpatient setting, while the rest of the cohort were referred to the clinic after already being on warfarin therapy as outpatients. Twenty-two patients were on enoxaparin at their first warfarin clinic visit. The median time between first and last warfarin clinic visits for the 73 patients was 182 days, with a maximum length of 1838 days. There were 911 warfarin clinic visits and the median number of visits was 10 per patient. Patients were judged to be adherent to warfarin at 78.0% of all visits (711/911). Ten patients were judged to be adherent at less than 50% of visits. At baseline, 3 of these 10 patients were positive for both cocaine use and injection drug use and 1 of the 10 was positive for alcohol abuse. In the univariable analysis of risk factors for study defined warfarin non-adherence, there were no variables with a statistically significant odds ratio (Table 2). The combined risk factors of cocaine use or injection drug use (OR 0.9, 95% CI 0.5–1.7, $p=0.78$) as

TABLE 2. UNIVARIABLE ANALYSIS OF BASELINE RISK FACTORS FOR WARFARIN NONADHERENCE (73 PATIENTS AND 911 VISITS)

<i>Risk factor</i>	<i>Warfarin adherent</i>	<i>Warfarin nonadherent</i>	<i>Number of clinic visits</i>	<i>Odds ratio (95% CI)</i>	<i>p Value</i>
Alcohol abuse					
Yes	185 (26.0%) ^a	46 (23.0%)	231	0.7 (0.4–1.3) ^b	0.26
No	526 (74.0%)	154 (77.0%)	680		
Cocaine use					
Yes	158 (22.2%)	39 (19.5%)	197	0.9 (0.5–1.7)	0.76
No	553 (77.8%)	161 (80.5%)	714		
Injection drug use					
Yes	57 (8.0%)	28 (14.0%)	85	1.5 (0.7–3.2)	0.30
No	654 (92.0%)	172 (86.0%)	826		
Mental illness					
Yes	160 (22.5%)	55 (27.5%)	215	0.8 (0.5–1.5)	0.57
No	551 (77.5%)	145 (72.5%)	696		
Combined risk ^c					
Yes	264 (37.1%)	82 (41.0%)	346	1.0 (0.5–1.8)	0.92
No	447 (62.9%)	118 (59.0%)	565		
Combined risk ^d					
Yes	182 (25.6%)	50 (25.0%)	232	0.9 (0.5–1.7)	0.78
No	529 (74.4%)	150 (75.0%)	679		
Hepatitis B/C					
Yes	117 (16.5%)	42 (21.0%)	159	1.4 (0.7–2.7)	0.39
No	594 (83.5%)	158 (79.0%)	752		
Age enrolled (per 10 years ↑)	43 ± 10 ^e	44 ± 10		1.0 (0.7–1.5)	0.92
Number of Clinic Visits	711 (78.0%)	200 (22.0%)	911		

^aFrequency (%).

^bWarfarin nonadherent relative to adherent.

^cCombined risk = alcohol abuse or cocaine use or injection drug use.

^dCombined risk = cocaine use or injection drug use.

^eMean ± standard deviation.

well as alcohol abuse or cocaine use or injection drug use (OR 1.0, 95% 0.5–1.8, $p=0.92$) were also not associated with study defined warfarin nonadherence.

On average, patients were prescribed HAART at 87.5% of visits, with 56 of 73 patients prescribed HAART at 100% of visits. Plasma HIV RNA levels were obtained at 28.0% of pharmacy clinic visits (255/911) and the result was <100 copies per milliliter at 59.2% of visits. In univariable analysis, adherence to warfarin therapy was associated with a lower risk of HIV RNA level ≥ 100 (OR 0.6, 95% CI 0.4–0.9, $p=0.01$) during the follow-up period. However, the baseline characteristics of alcohol abuse, cocaine use, injection drug use, hepatitis B or C, mental illness, or age at enrollment (per 10-year increase) were not associated with a statistically significant risk of HIV RNA ≥ 100 during follow-up pharmacy visits (Table 3). The combined risk factors of cocaine use or injection drug use as well as alcohol abuse or cocaine use or injection drug use were also not associated with HIV RNA ≥ 100 during the follow-up period.

Warfarin effectiveness and complications

Ten patients (16.7% of subjects with DVT/PE as initial indication for anticoagulation) experienced clinical recurrence of DVT with radiographic confirmation (9 patients with 1

recurrence and 1 patient with 2 recurrences). All 10 were African American/African men with a median age of 36 years, median CD4⁺ count of 232 cells per microliter, and median log HIV RNA of 2.9 at the time of recurrence. The median time to first recurrence was 1190 days (minimum, 41 days; maximum, 4031 days) and 7 of the 10 patients were on HAART at the time of recurrence. Hospitalization was required in 4 recurrences (median stay 8 days, maximum stay 25 days), but there were no deaths during recurrences. There were 2 recurrences in patients taking warfarin as directed but with subtherapeutic INR levels, 2 recurrences in patients who had stopped warfarin prematurely, and 2 recurrences in the setting of unknown anticoagulation (diagnosed at outside facilities). DVT recurred after completion of an appropriate course (at least 3–6 months) of anticoagulation in 4 patients. There was only 1 patient who developed a thrombosis recurrence despite being therapeutic on warfarin (INR 2.0 at diagnosis). This patient was treated with low molecular weight heparin and warfarin dosing was increased to a goal INR of 3.0 (range, 2.5–3.5). There were no subsequent thromboses in this patient.

Three subjects experienced a bleeding event while on warfarin (median dose 57.5 mg/week, median INR 6.3 at time of event). Each of the three episodes involved hematuria requiring hospital observation. None of the episodes required blood transfusion and none resulted in death. One of these

TABLE 3. UNIVARIABLE ANALYSIS OF BASELINE RISK FACTORS FOR PLASMA HIV RNA LEVEL ≥ 100 COPIES/PER MILLILITER (TOTAL 255 WARFARIN-ADHERENT VISITS)

Risk factor	VL ≥ 100	VL < 100	Number of clinic visits	Odds ratio (95% CI)	p Value
Alcohol abuse					
Yes	27 (26.0%) ^a	35 (23.2%)	62	1.2 (0.5–2.9) ^b	0.66
No	77 (74.0%)	116 (76.8%)	193		
Cocaine use					
Yes	31 (29.8%)	27 (17.9%)	58	1.8 (0.7–4.4)	0.20
No	73 (70.2%)	124 (82.1%)	197		
Injection drug use					
Yes	11 (10.6%)	20 (13.2%)	31	0.8 (0.2–3.1)	0.79
No	93 (89.4%)	131 (86.8%)	224		
Mental illness					
Yes	26 (25.0%)	40 (26.5%)	66	1.1 (0.4–2.6)	0.88
No	78 (75.0%)	111 (73.5%)	189		
Combined risk ^c					
Yes	45 (43.3%)	57 (37.7%)	102	1.2 (0.5–2.7)	0.63
No	59 (56.7%)	94 (62.3%)	153		
Combined risk ^d					
Yes	32 (30.8%)	39 (25.8%)	71	1.3 (0.5–3.1)	0.58
No	72 (69.2%)	112 (74.2%)	184		
Hepatitis B/C					
Yes	18 (17.3%)	29 (19.2%)	47	0.9 (0.3–2.6)	0.92
No	86 (82.7%)	122 (80.8%)	208		
Warfarin adherence ^e					
Yes	81 (77.9%)	129 (85.4%)	210	0.6 (0.4–0.9)	0.01
No	23 (22.1%)	22 (14.6%)	45		
Age enrolled (per 10 years $\uparrow$)	41 $\pm$ 8 ^f	43 $\pm$ 10		0.8 (0.5–1.2)	0.23
Number of Clinic Visits	104 (40.8%)	151 (59.2%)	255		

^aFrequency (%).

^bHIV RNA ≥ 100 relative to HIV RNA < 100 .

^cCombined risk = alcohol abuse or cocaine use or injection drug use.

^dCombined risk = cocaine use or injection drug use.

^eTime-dependent covariable.

^fMean $\pm$ standard deviation.

VL, viral load.

patients was not taking any warfarin-interacting medications, while one experienced an INR increase after a 14-day course of fluconazole. The third bleeding event occurred in a patient taking a stable regimen of four potentially warfarin-interacting drugs: atazanavir, ritonavir, clarithromycin, and trimethoprim-sulfamethoxazole.

Overall, the frequency of therapeutic INR levels during warfarin therapy was low, even when only including visits at which patients were judged to be adherent to warfarin. A therapeutic INR was recorded at 245 of these 711 adherent visits (34.5%, 95% CI 28.9–40.1%). The median percentage of visits with therapeutic INR while warfarin adherent was 30.8%. The median percentage of visits with subtherapeutic INR while warfarin adherent was 50.0%, while the median percentage of visits with supratherapeutic INR while warfarin adherent was 16.7%. The median number of warfarin dose changes per patient was 4 and the mean number of warfarin dose changes per patient was 5.7. For the total cohort, the mean INR at first warfarin clinic visit was 2.33 and the median was 1.89. For the 15 diagnosed as inpatients, the mean INR at first warfarin clinic visit was 2.56 and the median was 2.15. Changes in mean INR over time were not statistically significant ($p=0.17$). However, there was a trend in which the mean INR approaches 2.0 in months 3 through 6 during the follow-up period (Table 4). An analysis of INR longitudinal variability revealed that 92% of the estimated INR variance could be attributed to within-patient variance (as opposed to between-patient variance).

A univariable analysis yielded multiple factors that were associated with non-therapeutic INR (Table 5). A subsequent multivariable analysis (Table 6) showed that injection drug use at baseline was an independent risk factor for subtherapeutic INR (OR 2.4, 95% CI 1.3–4.7, $p=0.01$). Additionally, warfarin adherence was protective of both sub-therapeutic (OR 0.4, 95% CI 0.2–0.6, $p<0.0001$) and supratherapeutic (OR 0.5, 95% CI 0.3–0.9, $p=0.02$) INR status.

There were three PI/NNRTI-based regimens that were prescribed during at least 20 warfarin adherent clinic visits with goal INR 2.0–3.0 and thus were the focus of the warfarin dosing analysis: Lopinavir/ritonavir (LPV/RTV) 800 mg/200 mg total daily dose plus at least two nucleoside reverse

transcriptase inhibitors (≥ 2 NRTIs), efavirenz (EFV) 600 mg daily dose plus ≥ 2 NRTIs, and atazanavir/ritonavir (ATV/RTV) 300 mg/100 mg daily dose plus ≥ 2 NRTIs. LPV/RTV plus ≥ 2 NRTIs was prescribed for 18 patients for a total of 71 warfarin adherent visits, EFV plus ≥ 2 NRTIs was prescribed for 11 patients for a total of 35 warfarin adherent visits, and ATV/RTV plus ≥ 2 NRTIs was prescribed for 6 patients for a total of 21 warfarin adherent visits. Two of these patients received EFV followed by ATV/RTV. These two patients were excluded from the warfarin dosing analysis due to failure of the mixed effects linear model. Of the remaining 31 patients, those on LPV/RTV plus ≥ 2 NRTIs patients had therapeutic INR at 38.8% of visits, sub-therapeutic INR at 49.2% of visits, and supratherapeutic INR at 12.0% of visits. Patients on EFV plus ≥ 2 NRTIs had therapeutic INR at 33.3% of visits, sub-therapeutic INR at 37.2% of visits, and supratherapeutic INR at 29.5% of visits. Patients on ATV/RTV plus ≥ 2 NRTIs had therapeutic INR at 20.0% of visits, subtherapeutic INR at 45.0% of visits, and supratherapeutic INR at 35.0% of visits. The average weekly warfarin dose to maintain a therapeutic INR of 2.0–3.0 was significantly lower for patients on EFV plus ≥ 2 NRTIs compared to regimens based on either boosted PI. Specifically, the mean warfarin dose for therapeutic INR was 46 mg/week (95% CI 35–56 mg) for patients on EFV plus ≥ 2 NRTIs compared to 68 mg/week (95% CI 54–81 mg) for patients on LPV/RTV plus ≥ 2 NRTIs ($p=0.01$) and 71 mg/week (95% CI 57–85 mg) for patients on ATV/RTV plus ≥ 2 NRTIs ($p=0.007$).

Discussion

Given that the HIV-associated hypercoagulable state does not appear to resolve with antiretroviral therapy and given that conditions such as cardiac arrhythmias and valvular heart disease are not uncommon, HIV-infected individuals will continue to require long-term anticoagulation. With its narrow therapeutic window and multiple drug interactions, warfarin is challenging to administer even in the most closely monitored settings. Randomized trials of warfarin have yielded therapeutic INR levels at approximately 60% of follow-up visits.²⁵ In our study of HIV-infected individuals, 34.5% of warfarin adherent visits were associated with a therapeutic INR. Clearly, this is not optimal and was likely influenced by comorbidities and medication interactions. As shown in Table 1, over 20% of patients in our study had hepatitis B or C, and impaired liver function is a known risk factor for over-anticoagulation in the setting of vitamin K antagonist therapy.²⁶ While none of these patients had clinical manifestations of cirrhosis or histologic confirmation of cirrhosis on liver biopsy, it is possible that some of these patients had subclinical liver impairment that may have affected drug metabolism or INR levels while on warfarin. It is also possible that the presence of substance abuse as well as mental illness may have affected adherence reporting. To account for these comorbidities, we performed an analysis that compared patients with the baseline presence of hepatitis B or C, mental illness, or alcohol, cocaine, or injection drug abuse to those patients with none of these comorbidities. Patients without these comorbidities had therapeutic INR at almost 40% of adherent visits (145/368=39.4%, 95% CI: 34.4–44.4%). This compared to therapeutic INR in 100 of 343 adherent visits (29.2%, 95% CI: 24.3–34.0%) in the group with at least one of these

TABLE 4. MEAN INTERNATIONAL NORMALIZED RATIO VALUES OF ENTIRE COHORT OVER TIME

Month	Mean INR	Standard error	95% CI Lower	95% CI Upper
0	2.3267	0.1657	2.0008	2.6526
1	2.5109	0.1284	2.2583	2.7634
2	2.5519	0.1429	2.2708	2.8329
3	2.1048	0.1669	1.7766	2.4330
4	2.2495	0.1826	1.8904	2.6087
5	2.0469	0.2159	1.6223	2.4715
6	2.2225	0.2170	1.7958	2.6491
7	2.2561	0.2434	1.7775	2.7347
8	2.5946	0.3077	1.9897	3.1996
9	2.8165	0.2508	2.3234	3.3096
10	2.7302	0.3011	2.1381	3.3223
11	2.6025	0.2953	2.0218	3.1833
12	2.7344	0.3017	2.1411	3.3278

INR, international normalized ratio.

TABLE 5. UNIVARIABLE ANALYSES OF INTERNATIONAL NORMALIZED RATIO STATUS AMONG 73 HIV-INFECTED PATIENTS BY 6 BASELINE RISK FACTORS PLUS TIME-DEPENDENT WARFARIN ADHERENCE (911 PHARMACY CLINIC VISITS)

Risk factor	Subtherapeutic INR	Therapeutic INR	Supratherapeutic INR	Number of clinic visits	Odds ratio (95% CI)	p Value
Alcohol abuse						
Yes	123 (27.3%) ^a	60 (21.3%)	48 (26.8%)	231	1.4 (1.0–2.0) ^b	0.07
No	327 (72.7%)	222 (78.7%)	131 (73.2%)	680	1.4 (0.9–2.1) ^c	0.17
Cocaine use						
Yes	115 (25.6%)	47 (16.7%)	35 (19.6%)	197	1.7 (1.2–2.5)	0.005
No	335 (74.4%)	235 (83.3%)	144 (80.4%)	714	1.2 (0.7–2.0)	0.43
Injection drug use						
Yes	60 (13.3%)	13 (4.6%)	12 (6.7%)	85	3.2 (1.7–5.9)	0.0002
No	390 (86.7%)	269 (95.4%)	144 (93.3%)	826	1.5 (0.7–3.3)	0.34
Mental illness						
Yes	123 (27.3%)	53 (18.8%)	39 (21.8%)	215	1.6 (1.1–2.3)	0.01
No	427 (72.7%)	229 (81.2%)	140 (78.2%)	696	1.2 (0.8–1.9)	0.43
Combined risk ^d						
Yes	198 (44.0%)	82 (29.1%)	66 (36.9%)	346	1.9 (1.4–2.6)	<0.0001
No	252 (56.0%)	200 (70.9%)	113 (63.1%)	565	1.4 (1.0–2.1)	0.08
Combined risk ^e						
Yes	137 (30.4%)	54 (19.2%)	41 (22.9%)	232	1.8 (1.3–2.6)	0.0008
No	313 (69.6%)	228 (80.8%)	138 (77.1%)	679	1.3 (0.8–2.0)	0.33
Hepatitis B/C						
Yes	90 (20.0%)	37 (13.1%)	32 (17.9%)	159	1.7 (1.1–2.5)	0.02
No	360 (80.0%)	245 (86.9%)	147 (82.1%)	752	1.4 (0.9–2.4)	0.16
Warfarin adherence ^f						
Yes	324 (72.0%)	245 (86.9%)	142 (79.3%)	711	0.4 (0.3–0.6)	<0.0001
No	126 (28.0%)	37 (13.1%)	37 (20.7%)	200	0.6 (0.4–1.0)	0.03
Age enrolled (per 10 years ↑)	43 ± 10 ^g	43 ± 10	45 ± 10		1.0 (0.8–1.1)	0.59
					1.2 (1.0–1.5)	0.03
Number of clinic visits	450 (49.4%)	282 (31.0%)	179 (19.7%)	911		

^aFrequency (%).

^bSub-therapeutic INR relative to therapeutic-INR.

^cSupra-therapeutic INR relative to therapeutic-INR.

^dCombined risk = alcohol abuse or cocaine use or injection drug use.

^eCombined risk = cocaine use or injection drug use.

^fTime-dependent covariable.

^gMean ± standard deviation.

INR, international normalized ratio.

comorbidities. Thus, there was an odds decrease of 30.5% (OR: 0.695, 95% CI: 0.463–0.948, $p=0.079$) for therapeutic INR in patients with comorbidities. Another possible influence on therapeutic INR rates in this population is the high prevalence of impaired cognition, much of which is subclinical, in HIV-infected individuals despite antiretroviral therapy.²⁷ Decreased cognition is a known risk factor for lower adherence to warfarin therapy as measured by electronic pill cap testing.²⁸ It is possible that some of the patients in our study had subclinical neurocognitive deficits that affected their ability to take warfarin as directed or correctly remember the details of their adherence. Given all of these factors, closer warfarin monitoring may be warranted in the HIV-infected population.

In our study, injection drug use at baseline was the main independent risk factor for sub-therapeutic INR when adjusting for warfarin adherence and other variables. Not surprisingly, strict warfarin adherence was protective of both sub and supra-therapeutic INR. Warfarin adherence also appeared to be associated with fewer HIV RNA levels ≥ 100 copies per milliliter, which likely reflects better adherence to other medications that were concurrently prescribed. We found that to achieve therapeutic INR levels, approximately

50% more warfarin was required in patients on either lopinavir/ritonavir or atazanavir/ritonavir based regimens with NRTIs compared to patients on efavirenz with NRTIs. This dosing difference is likely explained by the differential effects of these antiretrovirals on warfarin metabolism.¹⁵ S-warfarin, the drug's most active enantiomer by fivefold, is predominantly metabolized by enzyme CYP2C9. The primary effect of efavirenz on CYP2C9 is inhibition, while lopinavir/ritonavir appears to induce the activity of CYP2C9. Therefore, it is not surprising that EFV is associated with lower warfarin dose to achieve therapeutic INR than LPV/RTV. Limited data is available on the effect of ritonavir-boosted atazanavir on warfarin metabolism, but our study shows that the weekly warfarin dose to achieve therapeutic INR for ATV/RTV-based regimens is higher than that for EFV and is similar to LPV/RTV.

Studies have shown that antibacterial agents (particularly trimethoprim-sulfamethoxazole) are the drugs that most profoundly affect anticoagulation during therapy with vitamin K antagonists.²⁹ During our study, there were 37 distinct periods of time during which patients were on trimethoprim-sulfamethoxazole, which thus represented the most commonly

TABLE 6. MULTIVARIABLE ANALYSIS OF INTERNATIONAL NORMALIZED RATIO STATUS AMONG 73 HIV-INFECTED PATIENTS ADJUSTED FOR 6 BASELINE RISK FACTORS PLUS TIME-DEPENDENT WARFARIN ADHERENCE (911 PHARMACY CLINIC VISITS)

Risk factor	Subtherapeutic INR	Therapeutic INR	Suprathreshold INR	Number of clinic visits	Odds ratio (95% CI)	p Value
Alcohol abuse						
Yes	123 (27.3%) ^a	60 (21.3%)	48 (26.8%)	231	1.2 (0.7–2.0) ^b	0.42
No	327 (72.7%)	222 (78.7%)	131 (73.2%)	680	1.2 (0.7–2.3) ^c	0.51
Cocaine use						
Yes	115 (25.6%)	47 (16.7%)	35 (19.6%)	197	1.3 (0.8–2.1)	0.23
No	335 (74.4%)	235 (83.3%)	144 (80.4%)	714	1.0 (0.6–1.8)	0.97
Injection drug use						
Yes	60 (13.3%)	13 (4.6%)	12 (6.7%)	85	2.4 (1.3–4.7)	0.01
No	390 (86.7%)	269 (95.4%)	144 (93.3%)	826	1.3 (0.6–3.1)	0.52
Mental illness						
Yes	123 (27.3%)	53 (18.8%)	39 (21.8%)	215	1.3 (0.9–2.0)	0.21
No	427 (72.7%)	229 (81.2%)	140 (78.2%)	696	1.0 (0.6–1.8)	0.88
Hepatitis B/C						
Yes	90 (20.0%)	37 (13.1%)	32 (17.9%)	159	1.1 (0.7–1.8)	0.69
No	360 (80.0%)	245 (86.9%)	147 (82.1%)	752	1.2 (0.7–2.2)	0.49
Warfarin adherence ^d						
Yes	324 (72.0%)	245 (86.9%)	142 (79.3%)	711	0.4 (0.2–0.6)	< 0.0001
No	126 (28.0%)	37 (13.1%)	37 (20.7%)	200	0.5 (0.3–0.9)	0.02
Age enrolled (per 10 years ↑)	43 ± 10 ^e	43 ± 10	45 ± 10		0.9 (0.8–1.1)	0.21
					1.2 (1.0–1.4)	0.07
Number of clinic visits	450 (49.4%)	282 (31.0%)	179 (19.7%)	911		

^aFrequency (%).

^bSubtherapeutic INR relative to therapeutic-INR.

^cSuprathreshold INR relative to therapeutic-INR.

^dTime-dependent covariable.

^eMean ± standard deviation.

INR, international normalized ratio.

prescribed warfarin interacting agent in our study. We included trimethoprim-sulfamethoxazole, in an exploratory model to determine its effect on warfarin dosing differences. This model showed that individuals on EFV plus ≥2 NRTIs still required less weekly warfarin than those on LPV/RTV plus ≥2 NRTIs (46 versus 67 mg, $p=0.01$) or those on ATV/RTV plus ≥2 NRTIs (46 versus 71 mg, $p=0.01$).

Of course, the possible confounders of warfarin therapy are too numerous to account for in a study of this size. Diet and genetic traits are known to affect anticoagulation during warfarin therapy and we were not able to account for these variables. Warfarin metabolism is affected by many other commonly used medications, a number of which are routinely used in the care of HIV-infected individuals. These include azole antifungals, fluoroquinolones, HMG-CoA reductase inhibitors, certain antidepressants, and others. We were not able to account for all potentially interacting medications in a study of this size. Additionally, we acknowledge that our definition of warfarin adherence (based on patient interview and pill pickup when available) may not have the same accuracy as other adherence measures such as pill count or pill cap data.³⁰

Given the challenges of warfarin therapy, it is not surprising that new oral anticoagulants have emerged. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, have been studied as anticoagulants for individuals with atrial fibrillation and also show promise for the treatment for DVT.^{31,32} Neither agent requires the frequent monitoring of warfarin, and dabigatran in particular appears to

have few interactions with antiretrovirals. These agents may soon prove to be more practical than warfarin for HIV-infected individuals who require long term anticoagulation.

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