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Fall Frequency among Men and Women with or at Risk for HIV Infection

Kristine M. Erlandson, MD, MS[*], **Michael W. Plankey, PhD**[†], **Gayle Springer, MLA**[‡], **Helen S. Cohen, EdD**[§], **Christopher Cox, PhD**[‡], **Howard J. Hoffman, MA**[‖], **Michael T. Yin, MD**[¶], and **Todd T. Brown, MD, PhD**[‡‡]

[*]Department of Medicine, Divisions of Infectious Diseases and Geriatric Medicine, University of Colorado, Aurora, CO 80045

[†]Department of Medicine, Division of Infectious Diseases, Georgetown University Medical Center, Washington, DC 20007

[‡]Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD 21205

[§]Bobby R. Alford Department of Otolaryngology–Head and Neck Surgery, Baylor College of Medicine, Houston, TX 77030

[‖]Epidemiology and Statistics Program, National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH), Bethesda, MD 20892

[¶]Columbia University Medical Center, Department of Medicine, Division of Infectious Diseases, New York, NY 10032

[‡‡]Department of Medicine, Division of Endocrinology, Diabetes, & Metabolism, Johns Hopkins University, Baltimore, MD, 21287

Abstract

Background—Falls and fall-related injuries are a major public health concern. HIV-infected adults have been shown to have a high incidence of falls. Identification of major risk factors for falls that are unique to HIV or similar to the general population will inform development of future interventions for fall prevention.

Methods—HIV-infected and uninfected men and women participating in a Hearing and Balance Sub-study of the Multicenter AIDS Cohort Study and Women's Interagency HIV Study were asked about balance symptoms and falls during the prior 12 months. Falls were categorized as 0, 1, or ≥ 2; proportional odds logistic regression models were used to investigate relationships between falls and demographic and clinical variables and multivariable models were created.

Results—24% of 303 HIV-infected participants reported ≥1 fall compared to 18% of 233 HIV-uninfected participants (p=0.27). HIV-infected participants were demographically different from

Corresponding author: Kristine M. Erlandson, 12700 E 19th Avenue; Mail Stop B168; Aurora, CO 80045, Phone 303-724-4941; Fax 303-724-4926, Kristine.Erlandson@ucdenver.edu.

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HIV-uninfected participants, and were more likely to report clinical imbalance symptoms ($p \leq 0.035$). In univariate analyses, more falls were associated with hepatitis C, female sex, obesity, smoking, and clinical imbalance symptoms, but not age, HIV serostatus, or other comorbidities. In multivariable analyses, female sex and imbalance symptoms were independently associated with more falls. Among HIV-infected participants, smoking, number of medications, and imbalance symptoms remained independent fall predictors while current protease inhibitor use was protective.

Discussion—Similar rates of falls among HIV-infected and uninfected participants were largely explained by a high prevalence of imbalance symptoms. Routine assessment of falls and dizziness/imbalance symptoms should be considered, with interventions targeted at reducing symptomatology.

Keywords

HIV; accidental fall; dizziness; vertigo; musculoskeletal equilibrium

INTRODUCTION

Falls and fall-related injuries are a major public health concern, with over one-third of adults aged 65 or older sustaining at least one fall annually, and approximately one-quarter of falls results in a serious injury (1, 2). Falls are the leading cause for fractures, loss of independence, non-fatal and fatal injuries among older adults (2-4). Adults aging with HIV have an increased prevalence of many fall-related risk factors, and we have previously found that the fall rate among middle-aged (45-65 years) HIV-infected adults on effective antiretroviral therapy (ART) mirrors that of uninfected adults aged 65 or older (5). Among older adults who have fallen, the fear of falling again is associated with poorer quality of life, increased frailty and depression, and subsequently results in less physical activity and social involvement, which can further exacerbate the underlying fall risks (6, 7). In addition to a high risk for falls and high frequency of falls, HIV-infected adults may be at a greater risk of sustaining an injurious fall or fracture due to underlying low bone density, low body weight, neuropathy, neurocognitive impairment and frailty (8-11). Indeed, the incidence of fractures is greater among HIV-infected compared to uninfected persons (12-14). With a growing number of older adults living with HIV, the impact of falls and fall-related complications has become increasingly relevant.

Identification of the major risk factors for falls among HIV-infected adults, whether unique to HIV-related characteristics or similar to fall risks in the general population, will inform the development of future interventions to reduce or prevent falls in older adults with HIV. The goals of this study were to 1) compare the fall rate in a population of men and women with HIV or at risk for HIV, 2) determine if HIV is an independent risk for falls, and 3) determine the contribution of other risk factors for falls that may be unique to HIV.

METHODS

The Multicenter AIDS Cohort Study (MACS) is a National Institutes of Health (NIH)-sponsored ongoing, prospective study of the natural and treated history of HIV infection

among men who have sex with men, established in 1984, and focused on four centers in Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA. A total of 6,973 men have or continue to participate in the semi-annual evaluations (15). The Women's Interagency HIV Study (WIHS) is a similar prospective study with a focus on women with or at risk for HIV, with 3,766 participants at 6 centers in New York City (Bronx and Brooklyn), NY; Chicago, IL; Los Angeles, CA; San Francisco, CA; and Washington, DC (16). Similar to the MACS, participants complete semi-annual evaluations with detailed interview, physical exam, and collection of blood for laboratory testing and storage. Self-reported use of antiretroviral medications is summarized at each visit to define prior and current use of highly active ART (HAART) (17).

All HIV-infected and HIV-uninfected men and women from the Baltimore/Washington, DC site of the MACS and Washington, DC site of the WIHS were considered for inclusion and screened for study participation. The exclusion criteria for the substudy was use of erectile dysfunction drugs and/or alcohol within 8 hours of testing. Eligible participants completed a questionnaire as part of the Hearing and Balance Substudy, between March 2008 and September 2010 (18, 19). The institutional review boards for each site approved the study, and all participants signed informed consent prior to participating.

Fall frequency was assessed as part of the Hearing and Balance Substudy Questionnaire by self-report: "During the past 12 months, about how many times have you fallen?", with a fall defined as unexpectedly dropping to the floor or ground from a standing, walking, or bending position. Falls were categorized as none, 1, and ≥ 2 falls in the prior 12 months. Clinical symptoms related to imbalance included self-report of the following symptoms: spinning or vertigo; feeling off-balance or unsteady; a floating, spacey, or tilting sensation; feeling lightheaded, without a sense of motion; and feeling as if one is about to pass out or faint. Floating, lightheadedness, and faint feeling were felt to represent the same underlying construct, and are difficult to distinguish clinically. To limit the number of variables in the model, these 3 reported symptoms were combined into a single variable for analyses. These symptoms were collected by self-administered questionnaire using wording identical to the sample adult questions in the 2008 National Health Interview Survey Dizziness and Balance Supplement (20, 21).

Demographic, behavioral, HIV-disease, and HIV treatment-related variables, physical and neuropsychological examination, quality of life, and depression questionnaires were obtained from the most recent semi-annual MACS/WIHS visit before the sub-study. Depressive symptoms were collected from the Centers of Epidemiology Study-Depression (CES-D), with depression defined as CES-D score of ≥ 16 (22). Number of recent medications included any medications in the last 5 days, excluding ART, birth control, or hormone replacement therapy (women only). Blood pressure medications included any reported use of antihypertensive agents. Hepatitis C was defined by detectable serum hepatitis C viral RNA or by the presence of hepatitis C antibody. Dyslipidemia was defined as fasting total cholesterol ≥ 200 mg/dL, low-density lipoprotein ≥130 mg/dL, high-density lipoprotein < 40 mg/dL, triglycerides ≥ 150 mg/dL, or use of lipid-lowering medications with self-report of a clinical diagnosis. Diabetes was defined as fasting glucose ≥ 126 mg/dL, self-report of a clinical diagnosis with use of medication, or a hemoglobin A1C of ≥

6.5%. Kidney disease was defined by an estimated glomerular filtration rate < 60 mL/min/1.73m^2 by the Modification of Diet in Renal Disease (MDRD) equation (23). Cognitive impairment was defined as two standard deviation worse than the HIV-uninfected, age, sex, and education-matched performance on two of three screening tests including Trails A, Trails B, and the Symbol Digit Modality Test (24, 25). Peripheral neuropathy was defined as < 10 second perception of vibration at either great toe using 120 Hz tuning fork (26). Body mass index (BMI) was calculated as kilograms divided by meters squared. Physical functional limitation was defined as "limited a lot" on vigorous activities on the Short Form (SF)-36 survey (27).

Statistical Analysis

Categorical variables (fall reasons) were compared using chi-square tests. The cross-sectional data were analyzed using two proportional odds logistic regression models using PROC LOGISTIC (SAS, Version 9.3, Carey, NC). The first model was designed to examine the relationship of HIV infection to number of falls (0, 1, >2). The second model was similar to the first model but for HIV-positive participants only. Univariate models were run for all covariates of interest. Covariates with a univariate p-value of ≤0.1 were included in the multivariable models along with variables controlling for age, gender, race, BMI, and HIV serostatus (HIV serostatus in first model only). In the models, BMI was included as both < 30 kg/m^2 and ≥ 30 kg/m^2, allowing for the regression line to differ for obese and non-obese. Covariables in the first multivariable model included depressive symptoms, vertigo, feeling off-balance, floating/lightheadedness/faint feeling. For models restricted to HIV-positive participants, additional covariables included a history of a clinical diagnosis of AIDS; current use of any HAART; current use of protease inhibitors (PI) or efavirenz; any (current or prior) use of zidovudine (AZT), didanosine (DDI), stavudine (D4T); current and nadir CD4 lymphocyte count; current HIV-1 RNA copies/mL; and whether HIV-1 RNA was less than the limit of detection (<200 copies/mL).

RESULTS

Of the 543 screened for eligibility, two were not eligible (recent use of erectile dysfunction drugs or alcohol) and two had missing screening data: 539 completed the Hearing and Balance Questionnaire. One had missing data and two did not know if they had fallen in the past year, thus 536 (303 HIV-infected, 233 HIV-uninfected) were included in the final analysis. The HIV-infected participants tended to be younger, female, black, had a lower BMI, used less alcohol, were current smokers, and had a greater frequency of many comorbid conditions in comparison to the HIV-uninfected participants (Table 1). Among the HIV-infected participants, the median CD4 cell count was 534 cells/μL, and 69% were on antiretroviral therapy with an HIV-1 RNA viral load level below the limit of detection. The majority of participants had received older ART regimens including zidovudine, stavudine, or didanosine.

Seventy-two (24%) of the HIV-infected participants reported at least one fall, and 39 (13%) reported 2 or more falls. Forty-two (18%) of the HIV-uninfected participants reported at least one fall, and 22 (9%) reported 2 or more falls. Participants most commonly reported

that they had “tripped or stumbled”, “slipped”, had “lost balance”, or “were not paying attention” before a fall. Of the reported conditions or reasons for a fall, HIV-infected participants were significantly less likely than HIV-uninfected participants to have reported that they “hurried too much” or “were not paying attention” as the reason for a fall ($p \leq 0.02$). Symptoms of vertigo (13% vs 8%); floating, lightheadedness, and/or faintness (22% vs 15%); and symptoms of feeling off-balance (22% vs 15%) occurred more commonly among HIV-infected compared to HIV-uninfected participants (Table 1).

Greater fall frequency was associated with female gender, obesity, smoking, HCV, and having clinical symptoms of vertigo, feeling off-balance, or feeling lightheaded, faint, or a floating sensation. The associations of age, HIV serostatus, or other comorbidities with falls were not statistically significant (Table 2). Among the HIV-infected participants only, greater fall frequency was associated with greater HIV-1 RNA viral load and fall frequency was lower with use of HAART, specifically with current protease inhibitor therapy. Greater fall frequency was not associated with clinical AIDS diagnosis, nadir or current CD4 lymphocyte count, HIV-1 RNA <200 copies/mL, or with other specific ART regimens (Table 2).

In multivariable analyses, being female and having symptoms of feeling off-balance or having symptoms of floating, lightheadedness and/or faintness were independently associated with greater self-reported falls. In multivariable analyses restricted to HIV-infected participants, smoking, the number of recent medications and symptoms of feeling off-balance, faint, or lightheaded remained independently associated factors related to greater falls, while current protease inhibitor use was associated with a lower likelihood of falls (Table 2).

DISCUSSION

In a combined cohort of men and women with or at risk for HIV infection, we found that 24% of HIV-infected and 18% of HIV-uninfected participants reported at least one fall in the prior year. Consistent with our prior findings in an HIV population (5), females had higher rates of falls than men in the overall population, even after adjusting for additional fall risk factors. In the multivariable analyses, HIV serostatus was not independently associated with falls, suggesting that the trend towards a higher fall rate among HIV-infected participants seen in previous studies may be due to an increased burden of fall risk factors such as comorbidities and greater number of medications (28, 29) rather than HIV itself, as seen by the lack of independent association with HIV serostatus, current or nadir CD4 count, viral load, or ART. Indeed, the strongest independent predictors of falls in both the overall and HIV-infected only persons were the symptoms of dizziness, lightheadedness, and feeling off-balance, which were reported more frequently among the HIV-infected men and women. These findings echo our prior findings, where impaired balance was associated with a 13-fold higher odds of recurrent falls among HIV-infected participants (5).

Among adults with or without HIV, impaired balance or dizziness is consistently one of the strongest predictors for increased falls and increased risk of injury following a fall (30-33). The increased prevalence of these imbalance symptoms in our HIV-infected participants

may explain the reason that falls were often due to trips, slips, or loss of balance, with significantly fewer falls among HIV-infected participants attributed to simple careless behaviors including “hurrying too much” or “not paying attention”. Although not assessed in the current study, prior literature has shown that older adults with dizziness have a markedly greater fear of falling (34), thus falls associated with imbalance symptoms could ultimately result in a greater fear of falling and further activity restriction.

Dizziness or lightheadedness were more frequently reported among HIV-infected participants in our cohort, and are commonly reported symptoms among HIV-infected participants in other populations: nearly 50% of HIV-infected veterans reported dizziness (35) and dizziness attributed to ART led to discontinuation (16%) or change (13%) of ART in WIHS participants (36). The underlying etiologies of dizziness in HIV are multifactorial. As a side effect of ART, dizziness occurs most frequently (13-28%) among efavirenz users (37, 38); however, we did not find an increased risk of falls among participants using efavirenz. Unrecognized drug-drug interactions between ART and cardiovascular medications, alpha-antagonist, or central nervous system acting agents may further contribute to dizziness or lightheadedness and falls (39). These drug-drug interactions are often most problematic with the protease inhibitors, thus the protective effect of protease inhibitor use on falls was surprising and has not been previously reported. We hypothesize this is a multifactorial effect from high central nervous system (CNS) penetration with low CNS or peripheral nervous system toxicity.

Prior studies have suggested higher rates of vestibular dysfunction among HIV-infected participants, particularly in more advanced HIV disease (40, 41), which may explain some of the frequent imbalance symptomology among our participants. However we did not find differences in objective testing of vestibular function between the HIV-infected and HIV-uninfected men and women in this same cohort (18), and found no association between falls and symptoms of vertigo in the current analysis. Prior studies have shown impairments in objective measures of imbalance in approximately 10% of middle-aged HIV-infected persons on effective ART (11, 42), with HIV-infected persons demonstrating poorer performance on objective laboratory or clinically-based imbalance measures compared to HIV-uninfected controls (43-45). Mild-to-moderate autonomic dysfunction may contribute to dizziness or lightheadedness, and appears to be more common in HIV infection than previously appreciated (46-48). In one study population, 61% of HIV-infected participants had objective testing consistent with autonomic dysfunction, and nearly half of the participants with objective autonomic dysfunction reported symptomatic lightheadedness or dizziness (46). A marked overlap between autonomic dysfunction and distal sensory neuropathy, an established complication of HIV and its therapy, suggests a similar underlying pathophysiology (46, 47). Although we did find a statistically significant association between falls and imbalance symptoms, we failed to find one with peripheral neuropathy. This could reflect a less sensitive measure of neuropathy, or that our participants were able to better compensate for peripheral neuropathy than older cohorts.

We recognize several limitations to our study. First, fall history was retrospectively collected, and may underestimate the actual number of falls (49, 50). Nevertheless, a recent comparison of fall recall and prospective fall collection among 600 older adults in Germany

found nearly identical incidence rate of falls, supporting the validity of retrospective fall history (51). Vestibular function in our cohort was previously assessed (18), but we did not have available, objective measures of autonomic function, balance or gait stability for the current study. Self-report of balance problems has been shown to be a stronger predictor for injurious falls than objective measures of balance in older adults (52) and had been associated with falls among middle-aged adults with disability (33) , thus our findings represent an important and clinically meaningful predictor of fall risk in HIV-infected persons. The MACS and WIHS cohort are not representative of the general population; instead, these cohorts were self-selected for presumed increased risk of acquiring HIV. The cohorts may not reflect the characteristics of individuals with recently acquired HIV infection. Illicit drug use was not included in this analyses, however Hepatitis C, smoking, and alcohol use provide a surrogate for exposure to additional substances that might increase fall risk Furthermore, the relatively small number of events limits the number of comparisons and multivariable adjustments, thus we acknowledge that other unadjusted or unrecognized confounders may have contributed to falls.

We have demonstrated a similar rate of falls among HIV-infected men and women compared to HIV-uninfected controls that is largely explained by a high prevalence of symptoms of dizziness, lightheadedness, and feeling off-balance, which were more frequent among the HIV-infected participants. Among middle-aged and older adults with or at risk for HIV infection, routine assessment of falls and symptoms of dizziness, lightheadedness, or balance difficulties should be strongly considered. Multifactorial fall reduction interventions have been successful in older adults (53), and the safety and efficacy of these components in reducing falls and fractures in HIV-infected adults should be further investigated. The role of vitamin D deficiency in fall risk and benefit of replacement in reducing falls is controversial and based primarily on observational data (54); vitamin D and fall risk or prevention has not been studied in an HIV population. Future targeted interventions to improve balance symptomatology may include exercise, balance training, more liberal blood pressure and blood glucose goals, elimination of certain medications, and/or changes in ART when applicable. The detrimental impact of falls on quality of life, morbidity, and mortality, make the prevention and reduction of falls a key priority in the care of middle-aged and older adults with and at risk for HIV infection.

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Table 1
Characteristics of HIV-uninfected and HIV-infected participants

	HIV-uninfected (N=233)			*HIV-infected (N=303)*			
	N	***%***	***Median (IQR)***	***N***	***%***	***Median (IQR)***	***P-value***
Clinical and Demographic Characteristics							
Age	.	.	54.9 (48,62)	.	.	49.7 (43,55)	<.0001
Female	42	18		141	47		<.0001
Black	71	30		199	66		<.0001
0 falls	191	82		231	76		0.27
1 fall	20	9		33	11		
2+ falls	22	9		39	13		
Body mass index	.	.	27.7 (24,33)	.	.	26.4 (23,31)	0.0058
Current Smoker	43	18		99	33		0.0002
≥ 14 alcohol containing drinks/week	23	10		8	3		0.0003
Self-reported physical function impairments	42	18		62	20		0.49
Comorbidities:							
Diabetes	35	15		54	18		0.39
Dyslipidemia	114	49		140	46		0.4171
Depressive symptoms	37	16		62	20		0.23
Kidney disease	26	11		75	25		<.0001
Neurocognitive impairment	4	2		17	6		0.0185
Peripheral neuropathy	48	21		63	21		0.8291
Prior stroke	6	3		10	3		0.62
HCV Positive	22	9		89	29		<.0001
Number of medications used in the past 5 days	.	.	2 (0,5)	.	.	2 (0,5)	0.14
Blood pressure medication use	71	30		106	35		0.27
Clinical Symptoms							
Vertigo *	19	8		40	13		0.062
Off-balance *	35	15		67	22		0.034
Floating, lightheadedness, and/or faint feeling *	34	15		66	22		0.035
HIV Characteristics (HIV –infected participants only)							
Current/prior clinical AIDS diagnosis			. .	85	28		.
Current use of HAART			. .	232	77		
Current use of efavirenz			. .	47	16		
Current use of protease inhibitor			. .	146	48		
Any use of AZT (zidovudine)			. .	190	63		
Any use of d4T (stavudine)			. .	160	53		
Any use of ddI (didanosine)			. .	137	45		
CD4+ lymphocytes (cells/μL)			. .		.	. 534 (358,719)	
CD4+ lymphocyte nadir (cells/μL)			. .		.	. 237 (120,334)	

	HIV-uninfected (N=233)			*HIV-infected (N=303)*			
	N	***%***	***Median (IQR)***	***N***	***%***	***Median (IQR)***	***P-value***
HIV-1 RNA below limit of detection (<200 copies/mL)	.	.		207	68		
HIV-1 RNA (copies/mL)						48 (40, 687)	

IQR = Interquartile range, specified by the 25^{th} and 75^{th} percentiles.

* self-report of symptoms within the last 12 months

Table 2

Proportional odds of falling 0, 1, or 2 or more times by demographic characteristics, comorbidities, symptoms, or HIV characteristics

Covariate of Interest	All participants Univariate proportional odds (95% CI)	*P value*	All participants Multivariate proportional odds (95% CI)	*P value*	HIV-infected only Multivariate proportional odds (95% CI)	*P value*
Age (by 10 years)	0.87 (0.71, 1.07)	*0.19*	1.01 (0.78, 1.31)	*0.98*	1.32 (0.91, 1.92)	*0.14*
HIV seropositivity	1.42 (0.93, 2.16)	*0.11*	0.99 (0.59, 1.67)	*0.98*		
Female	2.13 (1.41, 3.33)	***0.0003***	2.0 (1.12, 3.70)	***0.020***	2.0 (0.96, 4.17)	*0.064*
Black	1.13 (0.75, 1.70)	*0.56*	0.72 (0.4, 1.28)	*0.26*	1.12 (0.51, 2.46)	*0.78*
BMI <30 kg/m^2	0.98 (0.96, 1.0)	***0.026***	0.99 (0.97, 1.02)	*0.55*	1.0 (0.97, 1.03)	*0.94*
BMI ≥30 kg/m^2	1.00 (1.00, 1.00)	*0.90*	1.00 (1.0, 1.0)	*0.058*	1.00 (1.0, 1.0)	***0.046***
Current smoker	1.60 (1.02, 2.47)	***0.04***	1.57 (0.93, 2.65)	*0.089*	2.12 (1.11, 4.04)	***0.023***
≥14 alcohol containing drinks/week	1.60 (0.73, 3.51)	*0.24*				
Self-reported physical function limitations	1.30 (0.79, 2.15)	*0.30*				
Diabetes	1.17 (0.68, 2)	*0.57*				
Dyslipidemia	0.94 (0.59, 1.48)	*0.78*				
Depressive symptoms	1.61 (0.98, 2.63)	*0.059*	1.45 (0.85, 2.48)	*0.17*		
Kidney disease	1.32 (0.8, 2.18)	*0.28*				
Prior stroke	1.33 (0.44, 4.09)	*0.61*				
Neurocognitive impairment	1.40 (0.53, 3.72)	*0.50*				
Peripheral neuropathy	0.94 (0.56, 1.57)	*0.80*				
HCV positive	1.69 (1.05, 2.70)	***0.029***	1.31 (0.73, 2.34)	*0.37*		
# medications used in prior 5 days	1.05 (0.99, 1.11)	*0.13*			1.13 (1.01, 1.26)	***0.026***
Blood pressure medication use	1.03 (0.66, 1.6)	*0.91*				
Vertigo *	3.71 (2.15, 6.4)	***<0.0001***	1.31 (0.66, 2.59)	*0.44*	1.01 (0.42, 2.43)	*0.98*
Off-balance *	4.94 (3.13, 7.8)	***<0.0001***	2.48 (1.38, 4.43)	***0.0023***	2.87 (1.38, 6)	***0.0049***
Floating, lightheadedness, and/or faint feeling *	5.12 (3.25, 8.12)	***<0.0001***	2.75 (1.5, 5.04)	***0.001***	3.32 (1.51, 7.31)	***0.0028***
HIV –infected participants only †:						
On HAART	0.56 (0.31, 1)	***0.050***	--	--	0.67 (0.28, 1.59)	*0.36*
Current use of protease inhibitor	0.56 (0.33, 0.97)	***0.037***	--	--	0.40 (0.2, 0.81)	***0.011***

Covariate of Interest	All participants Univariate proportional odds (95% CI)	*P value*	All participants Multivariate proportional odds (95% CI)	*P value*	HIV-infected only Multivariate proportional odds (95% CI)	*P value*
Current use of Efavirenz	0.98 (0.58, 1.66)	0.93	--	--		
Log_{10} HIV-1 RNA copies/ml	1.26 (1.01, 1.57)	***0.043***	--	--	1.20 (0.88, 1.64)	*0.26*

p-values in bold indicate those reaching statistical significance (p<0.05); TIA, transient ischemic attack

*self-report of symptoms occurring in the past 12 months

†HIV-variables included in univariate analysis, but not found to be significantly associated with falls included any use of AZT, zidovudine; D4T, stavudine; DDI, didanosine, current and nadir CD4 lymphocyte count, and HIV-1 RNA < 200 copies/mL