Over-reported peripheral neuropathy symptoms in a cohort of HIV infected and uninfected Rwandan women: the need for validated locally appropriate questionnaires

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Abstract

Background: Peripheral neuropathy symptoms (PNS) are commonly manifested in HIV-infected (HIV+) individuals, although data are limited on the prevalence and predictors of PNS in HIV+ patients from sub-Saharan Africa.

Objective: To determine the prevalence and predictors of PNS in HIV+ and HIV-uninfected (HIV-) Rwandan women.

Methods: Data were analysed from 936 (710 HIV+ and 226 HIV-) women from the Rwanda Women Interassociation Study and Assessment (RWISA), an observational prospective cohort study investigating the effectiveness and toxicity of ART in HIV+ women.

Results: Of 936 enrolled, 920 (98.3%) were included in this analysis with 44% of HIV- and 52% of the HIV+ women reporting PNS (p=0.06). CD4+ count was not associated with PNS, although there was a non-significant trend towards higher prevalence in those with lower CD4+ counts. For the HIV- women, only alcohol and co-trimoxazole use were independently associated with PNS. WHO HIV stage IV illness and albumin ≤ 3.5 were associated with PNS in HIV+ women.

Conclusions: The rate of peripheral neuropathy symptoms reported in this cohort of HIV-infected African women seems implausible, and rather suggests that the screening tool for peripheral neuropathy in culturally diverse African settings be locally validated.

Keywords: Peripheral neuropathy symptoms, HIV and Rwandan women.

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Introduction

About 60% of patients with advanced HIV disease clinically develop evidence of neurological dysfunction during the course of their illness[1, 2]. Peripheral neuropathies, specifically sensory neuropathies, are the most common neuromuscular complications in HIV-infected (HIV+) patients. Peripheral neuropathy is common in HIV+ African populations, with prevalence ranging from 15% - 50%[3,4,5,6].

Several risk factors have been associated with peripheral neuropathy, including older age, advanced HIV disease and history of combination antiretroviral therapy (cART) or other neurotoxic drugs[7,8,9]. Although the introduction of cART has dramatically reduced mortality rates of people living with HIV infection, its use has been associated with increased peripheral neuropathy[10]. The antiretroviral agents most associated with peripheral neuropathy, are the "d" drugs: didanosine (ddI, rarely used), deoxycytosine (ddC, now not manufactured) and stavudine (d4T, very commonly used but has been reduced currently)[9]. The substantially improved life expectancy that cART creates for HIV infected individuals may be compromised by complications of therapy, including peripheral neuropathy. The aetiology of HIV- and cART-associated peripheral neuropathy symptoms is unclear, although the neurotoxic effects of cytokines, toxicity of HIV proteins and mitochondrial damage have been implicated[5].

However, although some studies have reported peripheral neuropathy, there are inadequate studies on predictors of peripheral neuropathy symptoms in HIV-infected African patients, where the burden of HIV infection is the highest, and cART is gradually becoming more available. As there are limited studies in African countries including Rwanda on the prevalence and predictors of peripheral neuropathy symptoms in HIV-infected individuals, there is a need to understand better factors associated with peripheral neuropathy symptoms in HIV-infected compared to HIV uninfected (HIV-) African individuals. We examined the prevalence of, and factors associated with peripheral neuropathy symptoms in antiretroviral-naïve HIV-infected and uninfected Rwandan women participating in the Rwanda Women's Interassociation Study and Assessment (RWISA). The findings from the study are important to inform policy on appropriate management of the disabling peripheral neuropathy symptoms particularly among women in whom HIV infection prevalence rate is highest in resource limited African countries including Rwanda.

Methods

Study Design and Setting

This was a cross-sectional analysis of enrolment data on the prevalence of, and factors associated with PNS among 936 (710 HIV+ and 226 HIV-) Rwandan women in the Rwanda Interassociation Study and Assessment (RWISA) study, enrolled in 2005 with follow-up visits every six months. RWISA was an observational prospective cohort study investigating the effectiveness and toxicity of ART in HIV-infected Rwandan women**.** Women who volunteered to participate were recruited from grassroots associations of people living with HIV infection attending various HIV clinics in Kigali. Participants were included if they were >25 years old, willing to undergo voluntary counselling and testing for HIV, present in Rwanda since 1994, and willing to return for follow-up; HIV-positive women were required to be naïve to ART, except for exposure to single-dose nevirapine to prevent mother-to-child HIV transmission. Each woman provided written informed consent. The study protocol was approved by the Rwanda National Ethics Committee and the Institutional Review Board of Montefiore Medical Center, Bronx, NY USA. At study entry, participants provided historical information including medical history, demographic parameters, psychosocial history, experience of trauma during the 1994 Rwandan genocide, and symptoms of depression and posttraumatic stress. A physical examination was performed and specimens were taken for CD4 count, full blood count, and other laboratory studies. Methods for the RWISA study have been previously described in detail[11].

Participants were interviewed by trained research nurses on several items including symptoms of peripheral neuropathy in the previous six months, ascertained by the validated question, "*In the past six months, have*

you experienced numbness, tingling, or burning sensations in your arms, legs, hands, or feet that lasted for more than two weeks?"[10]. Participants also provided socio-demographic characteristics, and a physical examination was performed. Blood specimens were taken for full blood count and CD4+ count determination measured at the National Reference Laboratory of Rwanda by FACS Count**.**

Statistical Analysis

Associations of peripheral neuropathy symptoms with HIV status and CD4+ counts were assessed by Fisher's exact and chi-square tests for categorical, and Kruskal Wallis tests for continuous variables. Separate univariate logistic regression models were fit to associations between predictor variables of interest, and peripheral neuropathy symptoms for HIV infected and uninfected women. For each HIV infection status group, the variables statistically significant at $p<0.1$ in the univariate model for the group were included in a multivariate logistic regression model for that group to further test for independent predictive associations with peripheral neuropathy symptoms.

Results

Participant Demographic Characteristics

Participants' demographic characteristics are illustrated in Table 1. Of 936 women who participated in the RWISA study, 920 (98.3%) had answered the peripheral neuropathy question, and were thus included in this analysis: 704 HIV+ and 216 HIV-.

Table 1: Demographic and Clinical Characteristics by HIV serostatus and CD4 cell count

Participant characteristics	HIV- women n=226	HIV+ women (n= 704)				All HIV+ women
		CD4>350 (n=195)	CD4 200-350 (n=267)	CD4<200 (n=242)	p-value*	
Age in years n (%)						
<30	34 (15)	51 (26)	50 (19)	57 (24)	<0.001	158(22)
30-40	59 (26)	105 (54)	150 (56)	133 (55)		388(55)
40+	133 (59)	39 (20)	67 (25)	52 (21)		158 (22)
Income/month/ Rwf N (%)						
<10k	91 (45)	66 (34)	98 (37)	87 (37)	0.07	251 (36)
10 – 35k	79 (39)	105 (54)	130 (49)	111 (47)		346 (50)
>35k	33 (16)	22 (11)	35 (13)	40 (17)		97 (14)
Education n(%)						
No schooling	67 (32)	46 (24)	58 (22)	52 (22)	0.16	156 (22)
Some primary school	68 (32)	78 (40)	98 (37)	92 (38)		268 (38)
Secondary or University	76 (36)	71 (36)	110 (41)	96 (40)		277 (40)
Marital status n (%)						
Legally married/partner	80 (38)	86 (44)	96 (36)	73 (30)	0.001	255 (36)
Widowed	107 (50)	71 (36)	118 (44)	107 (44)		296 (42)
Other	25 (12)	38 (10)	53 (20)	62 (26)		153 (22)
Body Mass index						
Blood Pressure mean±SD						
Systolic	119±15	117±9	117±11	115±11	0.009	116±10
Diastolic	74±10	72±7	71±8	71±8	0.02	71±7
Alcohol, n(%)	56 (28)	39 (21)	52 (20)	52 (22)		143 (21)
Smoking, n(%)	7 (3)	4 (2)	7 (3)	7 (3)		18 (3)
Albumin, mean±SD	3.9±0.5	3.6±0.6	3.5±0.7	3.3 ±0.7	<0.001	3.4±0.6
Creatinine, mean±SD	0.85±0.18	0.90 ±0.2	0.92 ±0.19	0.93±0.18	<0.001	0.92 ±0.19
Self-reported PNS n(%)	96 (44)	93 (48)	138 (52)	133 (55)	0.12	364 (52)
WHO stage 4 condition, n(%)	32 (15)	59 (30)	105 (39)	124 (51)	<0.001	228 (41)
Pulmonary TB, n(%)	4 (2)	20 (10)	28 (10)	44 (18)	<0.001	92 (13)
Any prior TB, n(%)	4 (2)	20 (10)	31 (12)	46 (19)	<0.001	97 (14)
Dapsone use		1 (1)	1 (0.4)	1 (0.4)	<0.001	3(0.4)
Bactrim use	41 (19)	145 (75)	246 (92)	220 (91)	<0.001	611 (87)
Albumin <3.5 gm/dL	44 (21)	75 (41)	130 (51)	146 (63)	<0.001	351 (52)
Creatinine >1.2 gm/dL	4 (2)	7 (4)	14 (6)	17 (7)	0.026	38 (6)
Isoniazid, prior use		8 (4)	15 (6)	20 (8)	<0.001	43 (6)

Data presented as n (%) or mean ±SD; 1 US$=600 Rwf; TB, tuberculosis; WHO World Health Organization; *the p-value refers to the 4-group difference (HIV-, CD4 > 350, CD4 200-350 and CD4 < 200)

The HIV+ women were younger than HIV- women (p<0.001). The HIV- women were more likely to be widowed (p=0.004), had higher systolic (p=0.045) and diastolic blood pressure (p=0.006), but were less likely to report prior pulmonary tuberculosis (p<0.001) than the HIV+ women (Table 1). Mean creatinine levels, having albumin <3.5 gms/dL (p<0.001) or creatinine > 1.0 mg/dL and any prior use of isoniazid (p<0.001) were higher in HIV+ women (Table 1).

Prevalence of peripheral neuropathy symptoms

Symptoms of peripheral neuropathy were reported by 44% of the HIV- and 52% of the HIV+ women (p=0.06). There was a statistically non-significant trend toward higher prevalence in HIV+ women with lower CD4+ in the categories >350, 200-350, and <200 cells/μl (48%, 52% and 55% respectively) (p=0.32).

Factors predicting peripheral neuropathy symptoms in HIV- women

Because of the unexpectedly high prevalence of reported PNS in the HIV- women, we developed separate statistical models for the HIV- and HIV+ women. Table 2 illustrates factors that predicted PNS in HIV- women in univariate and multivariate analysis. In univariate analysis, PNS in the HIV- women was associated with lower income, being reported by 55% and 27% of the women with income <10,000 FRW and >35,000 FRW respectively (p=0.02). But income was not independently associated with PNS among HIV- women in multivariate analysis (Table 2). Only alcohol and co-trimoxazole use were independently associated with PNS among HIV- women in multivariate analysis: alcohol [aOR= 2.40, 95% CI (1.22, 4.69), p=0.01] and co-trimoxazole [aOR= 2.25, 95% CI (1.08, 4.69), p=0.03] (Table 2).

Table 2: Univariate and multivariate associations of demographic and clinical characteristics with peripheral neuropathy in HIV uninfected women

Characteristic	Prevalence (%) of self-reported PNS (n=96)	Univariate Models		Multivariate Models	
		Univariate Odds Ratio (OR)	p-value	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Age/years (%)					
<30	11 (32%)		0.10		
30-40	22 (39%)	1.31		1.34 (0.51, 3.54)	0.56
40+	63 (50%)	2.12		2.11(0.83, 5.36)	0.12
Income					
< 10 k Rwf	50 (55%)		0.020		
10 - 35 k Rwf	34 (43%)	0.73		0.76 (0.39,1.47)	0.41
> 35 k Rwf	9 (27%)	0.36		0.87(0.13,1.01	0.05
Marital status (%)					
Legally married/ partner	33 (41%)		0.08		
Widowed	55 (51%)	1.56		0.89 (0.42, 1.85)	0.75
Other	7 (28%)	0.57		0.55 (0.19, 1.61)	0.28
Alcohol					
No	56 (38%)				
Yes	35 (62%)	2.68	0.002	2.40 (1.22, 4.69)	0.01
Albumin, per mg/dl					
n (mean ±SD)	91(3.89±0.47)	0.76	0.27		
Tuberculosis ever					
No	95 (45%)				
Yes	1 (25%)	0.41	0.43		
Cotrimoxazole use					
No	70 (40%)				
Yes	26 (63%)	2.60	0.007	2.25 (1.08, 4.69)	0.03
Creatinine >1.2 mg/ dl					
No	88 (43%)				
Yes	3 (75%)	3.96	0.20		

Table 3: Univariate and multivariate associations of demographic and clinical characteristics with peripheral neuropathy symptoms in HIV- infected women

Parameters	Prevalence (%) of PNS (n=364)	Univariate Models		Multivariate Models	
		Univariate Odds Ratio	p-value	Adjusted Odds Ratio (aOR) (95% CI)	p-value
CD4 count					
CD4 > 350	92 (48)		0.32		
CD4 200-350	138 (52)	1.17		1.08 (0.73, 1.60)	0.69
CD4 <200	133 (55)	1.34		1.05 (0.70, 1.58)	0.83
Age/years (%)					
<30	78 (49)		0.32		
30-40	201 (52)	1.10			
40+	85 (54)	1.19			
Income					
< 10 k Rwf	144 (57%)		0.09		
10 - 35 k Rwf	169 (48%)	0.73		0.90 (0.64,1.28)	0.56
> 35 k Rwf	47 (48%)	0.72		0.87 (0.51,1.41)	0.52
Level of education n (%)					
No schooling	97 (62)				
Some primary school	131 (49)	0.56	0.01	0.60 (0.40, 0.92)	0.02
Secondary or University	133 (48)	0.55		0.59 (0.39, 0.91)	0.02
Systolic (per 10 mg Hg)					
N (mean ±SD)	364(11.59 ±1.0)	0.936	0.40		
Diastolic (per 10 mg Hg)					
n (Mean ±SD)	364(7±0.73)	0.907	0.59		
Alcohol					
No	277 (52)				
Yes	71 (50)	0.911	0.62		
Smoking					
No	354 (52)				
Yes	10 (56)	1.171	0.74		
Albumin					
	345				
n (mean ±SD)	3.34±0.64	0.650	0.002		
WHO stage IV					
No	185 (44)				
Yes	179 (62)	2.05	<0.001	1.84 (1.33, 2.55)	≤0.001
Ever any TB					
No	306 (50)				
Yes	58 (60)	1.46	0.09	1.24 (0.78, 1.97)	0.36
Bactrim					
No	48 (53)				
Yes	315 (52)	0.95	0.83		
Albumin ≤3.5					
No	143 (45)				
Yes	202 (58)	1.69	<0.001	1.52 (1.10, 2.09)	0.01

Multivariate model does includes "any TB ever", but not "Pulmonary TB"

Factors that predicted PNS in HIV-positive women

Covariates associated with PNS were also assessed in HIV+ women in both univariate and multivariate models (Table 3). While there was no significant association of CD4+ count with PNS, other markers of advanced HIV disease progression demonstrated a strong independent association with PNS in multivariate analysis: WHO HIV stage IV [aOR; 1.84 95% CI (1.33, 2.55), p<0.001] and albumin ≤ 3.5 [aOR; 1.52 95% CI (1.10, 2.09), p= 0.01]. Educational attainment was lower in the women with PNS (no schooling; 62% vs 48%, p=0.01) in both unadjusted analysis and the multivariate model. Use of alcohol and co-trimoxazole were not statistically associated with PNS in the HIV+ women.

Discussion

We observed a strangely high prevalence of self-reported peripheral neuropathy symptoms in HIV-infected and uninfected Rwandan women. While peripheral neuropathy symptoms are common neurological complications of HIV infection[12,13] the high prevalence in both groups suggests possible over-reporting of peripheral neuropathy in this cohort. In particular, we believe it is unlikely that true peripheral neuropathy was present in 44% of HIV uninfected women. The item used to identify peripheral neuropathy symptoms, *"In the last six months have you experienced numbness, tingling, or burning sensations in your arms, legs, hands or feet that lasted for more than 2 weeks?"* may have not been specific to identify only peripheral neuropathy symptoms that occurred in the previous 6 months and lasted at least for 2 weeks. There is a cultural practice in Rwanda of describing "tired legs" as pain and numbness, and this may have resulted in misunderstanding of the assessment of peripheral neuropathy. Therefore, the feeling of "tired legs", often conceived as muscle cramps, may have been misconceived for peripheral neuropathy symptoms by the HIV uninfected women among whom the prevalence of peripheral neuropathy symptoms seem to have been over-reported.

Our own scepticism about the high prevalence of peripheral neuropathy symptoms among the HIV uninfected women prompted us to informally ask the nurses who conducted data collection to know whether the question on occurance of peripheral neuropathy was well understand, and interpreted well to participants during the study when the nurses conducted RWISA nurses-guided interviews. One additional probable reasons for this over reporting of peripheral neuropathy symptoms they suggested was that "….the peripheral neuropathy symptoms … *lasted for more than 2 weeks?"* was misunderstood for "…the peripheral neuropathy symptoms…*in the last 2 weeks?"* meaning perhaps something such as a single event of tingling due to poor circulation could have been misreported as peripheral neuropathy symptoms.

Our findings on the prevalence of peripheral neuropathy among the HIV-infected women are similar to a South African study in which the prevalence of peripheral neuropathy symptoms was 49%, and was associated with older age, use of ART and report of prior tuberculosis[14]. However, the South African study did not include HIV uninfected women for comparison, and may have similar over-reporting of peripheral neuropathy among the HIV-infected women. In spite of the potential over-reporting of peripheral neuropathy symptoms in HIV-uninfected participants in our study, the observed prevalence of self-reported peripheral neuropathy symptoms in the HIV-infected women is in agreement with other studies from both African and Western countries. Reports from Western countries suggest that the prevalence of peripheral neuropathy symptoms in HIV-infected individuals is within the range of 35 - 52%, and its prevalence in HIV-infected ART-naïve patients may be higher among those with lower CD4+ cell counts[12,13]. Our findings differ from one African study from Guinea-Bissau in HIV-infected and HIV-uninfected controls in which presence of peripheral neuropathy was predicted by older age and higher body mass index (BMI)[15]. However, the 45% reported prevalence of peripheral neuropathy symptoms reported in Guinea-Bissau is similar to our findings[15]. One study reported presence of peripheral neuropathy symptoms in 69% of HIV-infected patients using clinical examination, with only 33% prevalence of symptoms using more objective assessment with electro-neuromyography[13]. The prevalence of peripheral neuropathy for the HIV-infected women in our study is similar on average with the prevalence of peripheral neuropathy assessed by clinical examination and electro-neuromyography. [13] Noting this, it is interesting to observe that, if we had not included an HIV-negative cohort, our results would have been relatively unquestionable. Inclusion of a control group when using screening tools developed elsewhere may be a useful mechanism for ensuring valid results.

In the HIV-infected women, peripheral neuropathy

symptoms were not associated with HIV disease progression, as neuropathy symptoms were not related with CD4+ counts category. We observed a significant association of low serum albumin levels with presence of peripheral neuropathy symptoms in HIV-infected women. In a study population from New York, lower albumin levels were associated with a common type of peripheral neuropathy, the distal symmetrical polyneuropathy, which was reported in 38% of HIV-infected patients[16]. However, the study further reported an association of peripheral neuropathy symptoms with older age.[16] However, in the RWISA cohort, our group have previously reported that serum albumin was a marker of clinically more advanced HIV disease[17]. Similarly, HIV advanced disease (WHO Stage III and IV) was associated with greater peripheral neuropathy. The severity of HIV disease was also associated with distal sensory polyneuropathy in a Greek study in which WHO HIV stage IV illness and older age were associated with peripheral neuropathy symptoms[18].

Our study is limited by the investigators' concerns concerning the validity of the screening question, its cross-sectional design, and thus inability to make inferences about causality, especially as there was seemingly over-reporting of high rates of reported peripheral neuropathy in the HIV uninfected women. Secondly, our study was limited by its use of self-reported symptoms of peripheral neuropathy, rather than an objective assessment measure.

In conclusion, peripheral neuropathy symptoms are common in HIV-infected antiretroviral-naïve Rwandan women, when using this broad screening question. Due to potential for over-reporting of PNS symptoms, we suggest the use of more rigorous and culturally-specific assessment of peripheral neuropathy detection tools that would need to be validated and used in different and across African settings. Inclusion of HIV-uninfected controls will also help to determine if prevalence of HIV-associated peripheral symptoms are overestimated. If this is not feasible, then investigators must be cautious in interpreting self-reported symptoms across cultures.

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Conflict of interest:

None

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