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Peripheral neuropathy at first-line failure and on second-line in sub-Saharan Africa

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Background

Sensory peripheral neuropathy (SPN) remains one of the most common complications in HIV-positive patients despite the use of combination anti-retroviral therapy (cART) and effective virological control.

Little is known about prevalence of and risk factors for SPN in ART-experienced patients failing first-line ART or how SPN changes on protease inhibitor (PI)-based second-line ART in resource-limited settings.

Participants and Methods

The EARNEST trial was a large, open-label, randomised clinical trial performed in 14 centres in sub-Saharan Africa where HIV-positive adult and adolescent patients with first-line cART failure were randomised to lopinavir/ritonavir with either (i) 2-3 new or recycled NRTIs ("PI/NRTI"); (ii) raltegravir ("PI/RAL"); or (iii) raltegravir induction for the first 12 weeks only ("PImono").

We assessed PN using the ACTG Brief Peripheral Neuropathy Screen tool at baseline and weeks 48 and 96. Symptomatic PN (SPN) was defined as presence of bilateral neuropathic symptoms and abnormal signs. Asymptomatic PN (APN) was defined as abnormal signs without symptoms.

Factors associated with SPN were investigated using logistic regression with backward selection (exit criteria P>0.1). Centre effects were estimated pooling sites with similar overall prevalence (Table 1) to prevent perfect prediction in low prevalence sites. Primary analyses excluded 19 participants from the smallest centre that reported very high and potentially implausible rates of PN on symptom report (12/19; 63%) and abnormal signs (17/17 with completed PN signs, 100%).

Results

1251 participants had a complete PN assessment at baseline and were included in this analysis. In EARNEST 420 participants were randomised to PI/NRTI (TDF in 79%, ABC in 16%, ddI in 13%, d4T in <1%, 3TC/FTC in 87%), 422 to PI/RAL and 409 PImono second-line ART.

Results (cont)

SPN prevalence differed significantly between study sites However, it was similar in the three Kampala sites (25-28%) whereas the other six Ugandan sites, showed also similar but much lower prevalence (0-9%) suggesting that these differences may reflect true population differences.

Table 1: Characteristics at baseline by SPN status

	SPN (N=279)	no SPN (N=972)	Total (N=1251)	P
Demographic characteristics				
Female – n(%)	162 (58%)	564 (58%)	726 (58%)	0.99
Age - median (IQR)	41 (35-47)	36 (30-43)	37 (31-44)	<0.0001
CD4 cells/mm3				
Median (IQR)	55 (21-113)	76 (33-154)	71 (30-147)	<0.0001
Viral load copies/ml				
Median	81762	64529	67500	0.03
(IQR)	(29442-227600)	(21346-178978)	(22818-193000)	
ART history				
Years on combination ART - median (IQR)	4.3 (2.9-5.6)	3.9 (2.7-5.3)	4.0 (2.8-5.4)	0.06
Ever taken first-line – n(%)				
Nevirapine	252 (90%)	823 (85%)	1075 (86%)	0.02
Zidovudine	172 (62%)	682 (70%)	854 (68%)	0.007
Stavudine	199 (71%)	557 (57%)	756 (60%)	<0.0001
Tenofovir	31 (11%)	149 (15%)	180 (14%)	0.08
Laboratory parameters				
Haemoglobin g/dL –median (IQR)	11.7 (10.3-13.2)	12.2 (10.9-13.4)	12.1 (10.7-13.4)	0.02
Glucose mmol/L – median (IQR)	4.6 (4.3-5.0)	4.5 (4.1-4.9)	4.5 (4.2-4.9)	0.01
Creatinine mg/dL - median (IQR)	0.8 (0.6-1.0)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	<0.0001
Medical history				
Diabetes mellitus – n/total n(%)	7/279 (3%)	15/967 (2%)	22/1246 (2%)	0.29
Tuberculosis – n(%)	105 (38%)	225 (23%)	330 (26%)	<0.0001
CVD – n/total n(%)	29/279 (10%)	47/971 (5%)	76/1250 (6%)	0.001
Family history of CVD – n/total n(%)	63/218 (29%)	121/736 (16%)	184/954 (19%)	<0.0001
Alcohol consumption (ever) [b] – n/total	18/269 (7%)	95/823 (12%)	113/1092 (10%)	0.03
Smoke exposure (ever) [c] – n/total n(%)	55/278 (20%)	119/970 (12%)	174/1248 (14%)	0.002
Concomitant medication (last 10 weeks)				
Isoniazid – n(%)	42 (15%)	59 (6%)	101 (8%)	<0.0001
Ethambutol – n(%)	39 (14%)	54 (6%)	93 (7%)	<0.0001
Pyrazinamide – n(%)	34 (12%)	46 (5%)	80 (6%)	<0.0001
Rifampicin – n(%)	32 (11%)	47 (5%)	79 (6%)	<0.0001
Fluclonazole – n(%)	25 (9%)	61 (6%)	86 (7%)	0.12
Ciprofloxacin – n(%)	15 (5%)	27 (3%)	42 (3%)	0.04
Cotrimoxazole – n(%)	256 (92%)	906 (93%)	1162 (93%)	0.41
Socio-economic factors				
Employment status				
Available	279	967	1246	
Employed	161 (58%)	624 (65%)	785(63%)	<0.0001
Student	2 (1%)	95 (10%)	97 (8%)	
Unemployed- ill health	66 (24%)	109 (11%)	175 (14%)	
Unemployed- lack of jobs	50 (18%)	139 (14%)	189 (15%)	
Centre				
Kampala (JCRC)	60 (22%)	171 (18%)	231 (18%)	<0.0001
Kampala (IDI)	54 (19%)	161 (17%)	215 (17%)	
Kampala (Nsambya)	13 (5%)	34 (4%)	47 (4%)	
Zimbabwe	117 (42%)	146 (15%)	263 (21%)	
Others [d]	35 (13%)	460 (47%)	495 (40%)	

All p values from logistic regression. MFP was used for continuous variables to allow for non-linear relationships
[a] This table includes complete cases. Multivariable analysis is on multiply imputed data so includes an additional 6 participants who have missing symptomatic neuropathy status
[b] For model including units, p=0.49 for units of alcohol consumed in a week.
[c] Only 20 participants currently smoked so current and ex-smoker grouped into ever smokers.
[d] Site prevalence varies from 0%-11% in 9 sites with 31-97 participants per site. Site geographical locations were rural Uganda, Kenya, and Zambia

Results (cont)

Independent associations were found with age, female gender, history of TB, and higher levels of plasma creatinine. The odds of having SPN at first line failure were lower with higher CD4 counts and alcohol consumption, whereas smokers were more likely to have SPN at entry (Table 2).

When use of isoniazid in the last 10 weeks was included in the model as well as TB these were not independently associated with SPN, and TB was the better predictor of SPN. When substituting TB with isoniazid in the model, the effect of isoniazid was comparable to TB.

The prevalence of SNP was 11% and 17% at weeks 48 (p<0.0001 vs baseline) and 96 (p<0.0001 vs week 48, p=0.0002 vs baseline) respectively (Fig 1).

Isoniazid exposure remained strongly associated with SPN during the study period after adjustment by other factors (p<0.0001).

Table 2: Factors associated with SPN at first-line ART failure

	Unadjusted Odds ratio (95% CI)*	P	Adjusted Odds ratio (95% CI)	P
Sex- female	1.00 (0.76, 1.31)	0.99	1.65 (1.13, 2.41)	0.01
Age -years	1.05 (1.04, 1.06)	<0.0001	1.04 (1.02, 1.06)	<0.0001
CD4 (per doubling)	0.82 (0.76, 0.88)	<0.0001	0.83 (0.76, 0.92)	<0.0001
TB	2.00 (1.51, 2.66)	<0.0001	1.86 (1.33, 2.60)	<0.0001
Smoking exposure (ever)	1.76 (1.24, 2.51)	0.002	1.61 (1.02, 2.53)	0.04
Alcohol use	0.55 (0.33, 0.93)	0.03	0.54 (0.30, 0.96)	0.04
Creatinine (per 0.1mg/dl)	1.13 (1.07, 1.18)	<0.0001	1.09 (1.03, 1.16)	0.006
Centre				
Kampala (JCRC)	1	<0.0001	1	<0.0001
Kampala (IDI)	0.96 (0.62, 1.46)		0.82 (0.51, 1.33)	
Kampala (Nsambya)	1.09 (0.54, 2.20)		1.08 (0.48, 2.39)	
Zimbabwe	2.28 (1.56, 3.35)		1.07 (0.67, 1.70)	
Others †	0.22 (0.14, 0.34)		0.20 (0.12, 0.32)	
Viral Load (per doubling)	1.07 (1.00, 1.14)	0.03	1.07 (1.00, 1.15)	0.06
Glucose (per doubling)	1.63 (1.00, 2.66)	0.05	1.71 (0.96, 3.05)	0.07
Family history of CVD	2.07 (1.45, 2.94)	<0.0001	1.49 (0.98, 2.27)	0.06
Tenofovir exposure	0.69 (0.46, 1.04)	0.08	0.65 (0.40, 1.06)	0.08
Nevirapine exposure	1.69 (1.10, 2.61)	0.02	1.56 (0.95, 2.57)	0.08
Employment status				
Employed	1	<0.0001	1	0.07
Student	0.08 (0.02, 0.33)		0.35 (0.08, 1.53)	
Unemployed- too ill	2.35 (1.65, 3.33)		1.47 (0.97, 2.23)	
Unemployed- no jobs	1.39 (0.97, 2.01)		1.37 (0.90, 2.07)	

* contains only variables included in the multivariable model
† Site prevalence varies from 0%-11% in 9 sites with 31-97 participants per site. Site geographical locations were rural Uganda, Kenya, and Zambia

Fig. 1 Percentage of Patients with SNP during the study period by treatment arm

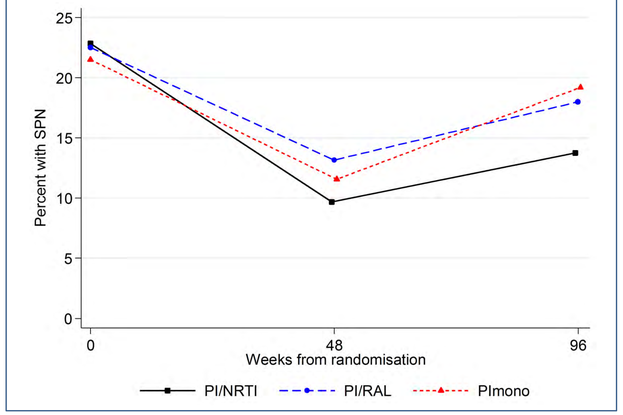


Table 3a: APN arm comparison

	PI/ NRTI n/total n (%)	PI/ RAL n/total n (%)	PImono n/total n (%)	P
Week 0	88/415 (21%)	85/422 (20%)	93/409 (23%)	
Week 48	90/391 (23%)	93/393 (24%)	101/388 (26%)	0.59
Week 96	117/377 (31%)	103/380 (27%)	105/376 (28%)	0.45

Table 3b: Abnormal signs suggestive of PN* arm comparison

	PI/ NRTI n/total n (%)	PI/ RAL n/total n (%)	PImono n/total n (%)	P
Week 0	184/415 (44%)	180/420 (43%)	182/409 (45%)	
Week 48	128/391 (33%)	145/398 (37%)	146/388 (38%)	0.30
Week 96	169/376 (45%)	173/380 (46%)	178/3756(47%)	0.79

*Regardless of the presence of symptoms

Conclusions

The prevalence of SPN in HIV-positive patients from Sub-Saharan Africa at the time of first-line failure and during PI-based second-line therapy was high.
In addition to well-recognised risk factors, SPN appeared to be strongly associated with isoniazid exposure used to treat TB episodes.
The potential contribution of the PI to maintaining the high rate of neuropathy observed during second-line therapy could not be ascertained from this study.

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