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Prevalence of peripheral neuropathy in antiretroviral therapy naïve HIV-positive patients and the impact on treatment outcomes—a retrospective study from a large urban cohort in Johannesburg, South Africa

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Abstract Peripheral neuropathy (PN) is associated with advanced HIV disease and may be a complication of antiretroviral therapy (ART) or anti-tuberculosis (TB) drugs, specifically isoniazid (INH). The effect of non-ART-drug-related PN on treatment outcomes is yet to be determined. We analysed prospectively collected cohort data for HIV-infected ART-naive adults initiating ART at the Themba Lethu Clinic, Johannesburg, South Africa from June 2004 to June 2009. Patients who presented with signs and symptoms of numbness or dysesthesia prior to initiation of ART were defined as having PN. Cox proportional hazard models were used to estimate the effect of PN alone (HIV-related PN) or PN with a history of INH use (TB-related PN) on mortality, lost to follow-up (LTFU), persistent and recurrent PN by 12 months of follow-up. Of the 9,399 patients initiating ART, 3.9 % had HIV-related PN while a further 1.8 % had TB-related PN. Patients with PN did not have a significantly higher risk of mortality compared to those without PN (hazard ratio (HR) 1.17 95 % CI 0.92–1.49). Patients with TB-related PN were less likely to be LTFU by 12 months (HR 0.65 95 % CI 0.44–0.97) compared to those without PN. Patients with HIV-related PN were at increased risk of persistent PN at 3 months post-ART initiation. Patients with HIV-related PN had a similar risk of recurrent PN compared to those with TB-related PN (HR 1.28 95 % CI 0.72–2.27). We demonstrate that patients with PN at initiation of ART present with advanced HIV disease. Completion of TB treatment may reduce the risk of persistent PN in patients with TB-related PN. Use of HIV drugs, even neurotoxic ones, may overall limit neuropathy.

Keywords Advanced HIV · Isoniazid (INH) · Late presenters · LTFU or mortality · Non-ART-drug-related PN · Tuberculosis (TB)

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Introduction

Since the early years of the epidemic in the developed world, HIV-1 infection has been shown to impact on both the central and peripheral nervous system (Robertson et al. 2011). Sensory neuropathies are the most frequent

neurological disorder associated with HIV infection and its treatment with antiretroviral therapy (ART) (Gonzalez-Duarte et al. 2007; Evans et al. 2011). Distal primary sensory polyneuropathy, often associated with severe pain and reduction in quality of life, has been reported to have a prevalence of up to 60 % in advanced HIV-1 disease (Simpson et al. 2006). There are two major types of HIV-associated distal sensory peripheral neuropathy (PN): primary HIV-associated and drug-related toxicity, together which affect approximately 30–67 % of patients with advanced HIV disease (Wuff et al. 2000). Little is known about the prevalence of PN in HIV-infected patients in resource-limited settings who have not received ART (Robertson et al. 2011) and the impact on treatment outcomes.

Neuropathy is a clinically significant problem in urban HIV-infected Africans, especially in older subjects with a history of prior tuberculosis (TB) infection (Maritz et al. 2010). Several factors increase the risk of developing PN; more advanced HIV disease or AIDS diagnosis, CD4 cell count <100 cells/mm^3, viral load above 10,000 copies/ml, past history of neuropathy, use of other neurotoxic drugs besides antiretrovirals (ARVs), certain nutritional deficiencies (vitamin B12 deficiency), history of prior TB infection, ageing associated with a deterioration in neurological function, co-existing medical conditions such as diabetes, hypertriglyceridemia or hepatitis C and heavy alcohol consumption (Gonzalez-Duarte et al. 2007; Evans et al. 2011; Maritz et al. 2010). Drugs such as isoniazid (INH) for TB treatment may contribute to the development of PN or worsen PN however the implications of such TB-related PN are unclear.

While PN is a well-described side-effect of neurotoxic drugs such as d4T (stavudine) and ddI (didanosine) there is limited published data on HIV-related PN in the ART-naïve population (Evans et al. 2011). We investigate PN as a marker of advanced HIV disease in resource-limited settings. We analyse data from a large urban cohort of ART-naïve individuals eligible for initiation of ART to determine the proportion and characteristics of patients who present with HIV- or TB-related PN. While PN has been associated with advanced HIV disease, the effect of HIV-related PN on treatment outcomes after initiation of ART is unclear. As PN has been associated with HIV infection, higher viral burden and underlying immune suppression, we anticipate poorer treatment outcomes in these patients compared to those without PN.

Furthermore, since INH may contribute to the development of PN or worsen PN, we investigated the effect of PN alone (HIV-related PN) or PN with a history of INH use (TB-related PN) on treatment outcomes within 12 months of initiating ART. In the developed world, several studies have demonstrated an improvement in peripheral nervous system function following ART initiation however the benefits for HIV-positive patients in resource-limited settings on different ART regimens are not known (Robertson et al. 2011). We investigate the effect of HIV- and TB-related PN on the persistence and recurrence of PN following ART initiation.

Since little is known about the proportion or characteristics of HIV-infected individuals who present late with advanced HIV disease (Kigozi et al. 2009), conditions such as HIV- and TB-related PN may help to identify patients in resource-limited settings that present late at clinics and those that should be “fast-tracked” for ART initiation.

Methods

Study site and subjects The study analysed prospectively collected data from a cohort of HIV-infected adults initiated on ART at Themba Lethu Clinic (TLC), Johannesburg. This cohort has been described elsewhere (Westreich et al. 2009a, b). Patients are initiated on standard public-sector first-line ART according to the South African National Department of Health guidelines if their CD4 cell count is <200 cells/mm^3 irrespective of World Health Organization (WHO) stage or they have a WHO stage IV defining illness, irrespective of CD4 count (DOH Guidelines 2004). ART-eligible patients are assessed by a physician prior to initiating treatment. Patient data is extracted from an electronic patient management system called TherapyEdge-HIV^{TM} (Associated Biological Systems, South Africa).

Eligibility criteria Eligible HIV-positive subjects were ART naïve, ≥18 years of age, had a CD4 cell count at ART initiation <200 cells/mm^3 and were initiated onto a standard first-line regimen of stavudine (d4T) or zidovudine (AZT) with lamivudine (3TC) and either efavirenz (EFV) or nevirapine (NVP) between June 2004–June 2009 (Westreich et al. 2009b; Brennan et al. 2010; Fox et al. 2010). To exclude other causes of PN, patients with co-existing medical conditions at ART initiation such as diabetes, hypertriglyceridemia (defined as a triglyceride [TG] >500 mg/dL), or hepatitis C were excluded from the PN strata, although hepatitis C co-infection is rare in South Africa and ranges from 1.9 % (Amin et al. 2004) to 6.4 % (Parboosing et al. 2008). Statistical models were adjusted for other factors such as age, past history of PN and alcohol consumption.

Diagnosis and definitions The main exposure of interest was recorded PN prior to initiation of ART. Diagnosis of PN was made by standard examination which included symptom review as it is not standard of care to perform neurological exams in the government HIV clinic setting due to limited capacity and resources (Menezes et al. 2011). Patients who presented with clinical signs and symptoms of numbness, dysesthesia, burning sensation or stabbing pain prior to initiation of ART were defined as having peripheral

neuropathy, once other causes were excluded (Menezes et al. 2011). Clinicians are intensively trained in the history, clinical presentation, examination and treatment of conditions such as PN. The clinical team at this site is supported and assisted by highly experienced specialist HIV and infectious diseases consultants. Clinicians at TLC recognize and diagnose PN and enter the diagnosis and medications prescribed onto an electronic patient management system called TherapyEdge-HIV^{TM}. The recorded condition, icd10 code, start and stop date of condition and medications prescribed can be obtained from the database and verified by paper files for the study period.

Individuals were classified as having HIV-related PN at initiation if a clinical diagnosis of PN was recorded between 90 days prior to and 7 days post-ART initiation (baseline). Patients were classified as having TB-related PN if a clinical diagnosis of PN was recorded at ART initiation after TB diagnosis and treatment (with INH; median dose 206 mg interquartile range (IQR) 180–240 once daily) within 6 months prior to initiating ART.

We estimated two outcomes. Firstly, we compared the effect of PN at ART initiation on loss to follow-up and all-cause mortality within 12 months of initiating ART. Loss to follow-up (LTFU) was defined as having missed a clinic appointment (i.e. clinical assessment or ARV pickup) by at least 3 months after the scheduled visit date (Brennan et al. 2010). All-cause mortality is ascertained via South Africa's National vital registration system (Fox et al. 2010; Fairall et al. 2008; Boulle et al. 2010). The dataset was closed on 31 May 2010 allowing a minimum potential follow-up time of 12 months for all study subjects. Person time accrued from ART initiation until the earliest of: (1) outcome of interest (death or LTFU), (2) completed 12 months of follow-up or (3) close of dataset on 31 May 2010. Patients who transferred to another facility were censored at their last clinic visit. Time on ART (in months) was calculated from start of ART until the earliest of death, LTFU, transfer out or close of dataset.

The second analysis was restricted to patients with PN at ART initiation. We estimated the effect of HIV-related PN on persistent or recurrent PN compared with those with TB-related PN. Persistence of PN was defined as a recorded stop date more than 3 months after ART initiation (the stop date is recorded by the clinician at the next medical visit if the patient no longer presents with signs and symptoms of the condition). Person time accrued from ART initiation until the earliest of: (1) death, (2) LTFU, (3) transfer out, (4) stop date of PN, or (5) close of dataset on 31 May 2010. Sixty-four patients had no stop dates recorded for PN after initiation of ART so a sensitivity analysis was performed which classified patients with a missing stop date as either (1) not having persistent PN or (2) having persistent PN.

Recurrent PN was defined as having a clinical diagnosis of PN at least 30 days after recorded stop date of first PN diagnosis. Person time accrued from recorded stop date of first PN diagnosis until the earliest of: (1) death, (2) LTFU, (3) transfer out, (4) recurrent clinical diagnosis of PN, or (5) close of dataset on 31 May 2010.

Statistical analysis Patient characteristics at initiation of ART were stratified into the following groups: (1) No PN, (2) HIV-related PN or (3) TB-related PN (Table 1). Groups were compared using Student *t* test or Kruskal–Wallis for continuous variables and Chi-square (χ^2) test for proportions (p value <0.05 was considered significant). Kaplan–Meier curves and log-rank test were used to compare ART outcomes (mortality, LTFU by 12 months follow-up as well as persistence and recurrent PN) between the groups. We estimated crude and adjusted hazard ratios (HR) of the ART outcomes using Cox proportional hazard models (Table 2). Factors such as age, gender, CD4 count, haemoglobin (Hb), body mass index (BMI), alanine aminotransferase (ALT) at initiation of ART, history of PN >90 days prior to ART initiation, alcohol consumption and d4T drug containing regimen were included in adjusted models where appropriate. All analyses were performed using the SAS® 9.1 statistical software package (SAS Institute, Inc., North Carolina, USA).

Use of Themba Lethu Clinic data was approved by the Human Research Ethics Committee of the University of the Witwatersrand (HREC M110140/M060626).

Results

Of a total of 18,272 HIV-positive individuals ever initiated on ART at TLC, we excluded those who were ART experienced at presentation to the clinic (n=2,694), less than 18 years of age (n=98), were not initiated onto a standard first-line regimen (n=1,601) or were initiated on ART outside the study period June 2004–June 2009 (n=4,480). The remaining 9,399 subjects were included in the analysis (Table 1). Of these, a total of 5.7 % (540/9,399) had a clinical diagnosis of PN at ART initiation, 1.2 % (112/9,399) had a prior history and a further 18.3 % (1,724/9,399) developed PN after ART initiation.

Characteristics at ART initiation

Patients with PN at ART initiation were similar to patients without PN in terms of education (34 vs. 35 %; p=0.508), median ALT (27 vs. 23 IU/L; p=0.568), median MCV (88 vs. 87 fL; p=0.757), age <40 years (36 vs. 34 %; p=0.366) and history of alcohol use (9 vs. 11 %; p=0.116). Patients with PN were predominantly male (46 vs. 38 %; $p<0.0001$) and unemployed (61 vs. 56 %; p=0.026) with lower median CD4 (59 vs. 73 cells/mm^3; p=0.04), lower median

Table 1 Baseline characteristics and outcomes of 9,399 patients, presenting with HIV-related PN or TB-related PN, initiated on ART from an HIV urban site (Themba Lethu Clinic, Johannesburg, South Africa)

Baseline characteristics		No PN *N*=8,859 (94.3 %)	HIV-related PN *N*=370 (3.9 %)	TB-related PN *N*=170 (1.8 %)
Age at initiation (years)	Median (IQR)	36.1 (31.2–42.5)	37.7 (32.7–43.8)	35.8 (31.1–40.7)
	≥40 years	2,978 (34 %)	146 (39 %)	46 (27 %)
Gender	Female	5,535 (62 %)	209 (56 %)	80 (47 %)
	Male	3,324 (38 %)	161 (44 %)	90 (53 %)
Employed	Yes	3,909 (44 %)	144 (39 %)	64 (38 %)
Education	Completed 2nd school	3,010 (35 %)	121 (33 %)	60 (36 %)
Ethnic group	African	8,430 (95 %)	361 (98 %)	166 (98 %)
History of alcohol use	Yes	980 (11 %)	30 (8 %)	18 (11 %)
BMI (kg/m^2)	Median (IQR)	21.2 (18.8–24.3)	20.2 (18.0–23.4)	19.2 (17.6–21.5)
	<18.5 kg/m^2	1,689 (22 %)	92 (29 %)	61 (40 %)
Haemoglobin (g/dL)	Median (IQR)	11.4 (9.9–12.9)	10.8 (9.3–12.4)	10.4 (9.0–11.6)
	<10 g/dL	2,167 (26.1 %)	131 (36.6 %)	66 (50.0 %)
MCV (fL)	Median (IQR)	88 (83–92)	88 (84–93)	88 (83–93)
	>100 fL	256/7,984 (3 %)	19/345 (6 %)	6/157 (4 %)
Liver transaminase	AST (median, IQR)	34 (27–48)	38 (29–55)	44 (34–58)
	ALT (median, IQR)	23 (17–35)	26 (18–40)	28 (20–38)
	ALT >45 IU/L	1,238 (15 %)	67 (19 %)	27 (17 %)
CD4 count (cells/mm^3)	Median (IQR)	73 (27–133)	60 (20–123)	57 (21–103)
	<50 cells/mm^3	3,347 (38.7 %)	165 (45.4 %)	73 (43.2 %)
	51–100 cells/mm^3	1,992 (23.1 %)	75 (20.7 %)	53 (31.4 %)
	101–200 cells/mm^3	3,299 (38.2 %)	123 (33.9 %)	43 (25.4 %)
Viral load (copies/ml)	Median (IQR)	25,000 (13,000–46,000)	29,000 (14,000–46,000)	24,500 (15,000–43,000)
Log_{10}		4.4 (4.1–4.7)	4.5 (4.1–4.7)	4.4 (4.2–4.6)
Clinical stage	Stages I and II	3,832 (56 %)	133 (45 %)	16 (12 %)
	Stages III and IV	3,011 (44 %)	162 (55 %)	120 (88 %)
First-line ART regimen	AZT/3TC/EFV	166 (1.8 %)	58 (15.7 %)	31 (18.2 %)
	AZT/3TC/NVP	17 (0.2 %)	–	–
	d4T/3TC/EFV	7,989 (90.2 %)	299 (80.8 %)	139 (81.8 %)
	d4T/3TC/NVP	687 (7.8 %)	13 (3.5 %)	–
Outcomes by 12 months follow-up				
Alive and in care	*n* (%)	4,923 (55.6 %)	196 (53.0 %)	100 (58.8 %)
Lost to follow-up	*n* (%)	1,998 (22.5 %)	77 (20.8 %)	32 (18.8 %)
Transferred out	*n* (%)	822 (9.3 %)	41 (11.1 %)	13 (7.7 %)
Death	*n* (%)	1,116 (12.6 %)	56 (15.1 %)	25 (14.7 %)
Time on ART (months)	Median (IQR)	26.6 (12.3–46.1)	24.6 (7.7–40.3)	29.2 (14.3–44.9)
Change in regimen	*n* (%)	844 (9.5 %)	50 (13.5 %)	35 (20.6 %)
Reason for regimen change				
Peripheral neuropathy	*n* (%)	14 (25.4 %)	22 (44.0 %)	18 (51.4 %)
Fat redistribution	*n* (%)	65 (7.7 %)	2 (4.0 %)	3 (8.6 %)
Pregnancy	*n* (%)	43 (5.1 %)	2 (4.0 %)	3 (8.6 %)
Toxicity	*n* (%)	38 (4.5 %)	2 (4.0 %)	2 (5.7 %)
Other/not specified	*n* (%)	484 (57.3 %)	22 (44.0 %)	9 (25.7 %)

Variables are proportions (*n*, %) unless otherwise specified.

ART antiretroviral therapy, *BMI* body mass index, *MCV* mean cell volume, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *IQR* interquartile range

Table 2 Cox proportional hazard ratio for death and LTFU by 12 months post-ART initiation and persistent or recurrent PN—stratified by HIV-related PN and TB-related PN among ART patients in Johannesburg, South Africa (n=9,399)

	N with outcome	Person time	Rate/100 pys	Crude HR (95 % CI)	Adjusted HR (95 % CI)[a]
Mortality[b] by 12 months post-ART initiation					
No PN	1,116 (12.6 %)	7,587.0	14.7	1.0	1.0
TB-related PN	25 (14.7 %)	148.1	16.9	1.14 (0.77–1.69)	1.10 (0.73–1.65)
HIV-related PN	56 (15.1 %)	301.8	18.6	1.26 (0.96–1.65)	1.21 (0.91–1.60)
Lost to follow-up[c] by 12 months post-ART initiation					
No PN	1,998 (22.5 %)	7,587.0	26.3	1.0	1.0
TB-related PN	32 (18.8 %)	148.1	21.6	0.81 (0.57–1.14)	0.65 (0.44–0.97)
HIV-related PN	77 (20.8 %)	301.8	25.5	0.98 (0.78–1.23)	1.02 (0.79–1.31)
Persistence of PN[d] >3 months after ART initiation					
TB-related PN[e]	103 (60.6 %)	158.7	64.9	1.0	1.0
HIV-related PN[e]	205 (55.4 %)	268.1	76.5	1.24 (0.97–1.57)	1.40 (1.07–1.84)
TB-related PN [f]	128 (75.3 %)	158.7	80.7	1.0	1.0
HIV-related PN[f]	244 (65.9 %)	268.1	91.0	1.23 (0.99–1.53)	1.34 (1.04–1.72)
Recurrent PN[g] post-ART initiation					
TB-related PN	26 (15.3 %)	350.9	7.4	1.0	1.0
HIV-related PN	60 (16.2 %)	678.9	8.8	1.15 (0.71–1.85)	1.28 (0.72–2.27)

HR hazard ratio, *CI* confidence interval, *pys* person years

[a] Adjusted for CD4 count, ALT, BMI, Hb, past history of PN, d4T containing regimen, age and gender at ART initiation

[b] Mortality obtained from South African National Vital Registration Infrastructure Initiative

[c] Lost to follow-up defined as ≥4 months since last visit

[d] Persistence of PN defined as stop date >3 months after ART initiation

[e] Patients with missing stop date were assumed not to have developed the outcome or as not having persistent PN

[f] Patients with missing stop date were assumed to have developed the outcome or as having persistent PN

[g] Clinical diagnosis of peripheral neuropathy at least 30 days after recorded stop date of first PN diagnosis

haemoglobin (10.6 vs. 11.4 g/dL; $p<0.0001$) and lower median BMI (19.8 vs. 21.2 kg/m^2; $p<0.0001$) compared to patients without PN. Patients with PN had higher median aspartate transaminase (AST; 39 vs. 34 IU/L; $p=0.004$) and were more frequently classified as WHO clinical stage III/IV (65 vs. 44 %; $p<0.001$) while fewer were prescribed a stavudine (d4T) containing regimen (84 vs. 98 %; $p<0.001$) compared to patients without PN.

Of the 540 patients that had a clinical diagnosis of PN at ART initiation, 69 % (370/540) had PN without a history of TB and were classified as HIV-related PN while the remaining 31 % (170/540) had PN and a history of TB and were classified as TB-related PN. Both groups were similar in terms of employment ($p=0.679$), ethnic group ($p=0.955$), education ($p=0.380$), history of alcohol use ($p=0.347$), median AST ($p=0.094$), median ALT ($p=0.421$), median MCV ($p=0.997$) and first ART regimen ($p=0.457$) containing d4T however the TB-related PN patients were predominantly male (53 vs. 44 %; $p=0.041$), slightly younger (<40 years of age; 73 vs. 61 %; $p=0.005$) had lower median BMI (19.2 vs. 20.2 kg/m^2; $p=0.008$), lower median haemoglobin (10.4 vs. 10.8 g/dL; $p=0.076$) and lower median CD4 cell count (57 vs. 60 cells/mm^3; $p=0.025$) compared to HIV-related PN patients. Median time on ART for the HIV-related PN group was 24.6 months (IQR 7.7–40.3) and 29.2 months (IQR 14.3–44.9) for the TB-related PN group.

Patient retention

By 12 months on ART, 196 (53.0 %) of the HIV-related PN patients were still in care, 77 (20.8 %) were LTFU, 41 (11.1 %) transferred to another facility and a further 56 (15.1 %) had died. Among the TB-related PN group, 100 (58.8 %) were still in care, 32 (18.8 %) were LTFU, 13 (7.7 %) transferred to another facility and a further 15 (14.7 %) had died. Of patients with HIV-related PN and TB-related PN, 60 (16.2 %) and 26 (15.3 %) had a recurrent diagnosis of PN within 12 months of follow-up, respectively.

Mortality and LTFU

Rates of mortality were highest amongst patients with PN (18.0/100 person years (pys)) compared to patients without

PN at ART initiation (14.7/100 pys). Rates of LTFU were lowest amongst patients with PN (24.2/100 pys) compared to patients without PN at ART initiation (26.3/100 pys). Adjusted hazard ratios suggest that patients with PN at ART initiation may be at increased risk of mortality (hazard ratio (HR) 1.17 95 % CI 0.92–1.49) compared to those without PN. However, patients with PN at ART initiation were less likely to be LTFU by 12 months post-ART initiation (HR 0.88 95 % CI 0.71–1.09) compared to those without PN, though both these estimates were imprecise and lacked precision.

Despite that the differences were not statistically significant, crude Kaplan–Meier survival curves showed that HIV-related PN patients had the highest risk of mortality (log-rank test p=0.184) while TB-related PN had the lowest risk for LTFU (log-rank test p=0.226; Fig. 1).

The point estimate for mortality risk was higher among patients with HIV-related PN (HR 1.21 95 % CI 0.91–1.60) than TB-related PN (HR 1.10 95 % CI 0.73–1.65) when compared to patients without PN. In adjusted models, males (HR 1.26 95 % CI 1.11–1.42), those >40 years of age (HR 1.31 95 % CI 1.16–1.48), those with lower CD4 count (≤50 vs. >100 cells/mm^3; HR 2.60 95 % CI 2.23–3.02 or 50–100 vs. >100 cells/mm^3; HR 1.52 95 % CI 1.26–1.82), those with low haemoglobin (<10 vs. ≥10 g/dL; HR 1.92 95 % CI 1.69–2.18), low BMI (<18.5 vs. ≥18.5 kg/m^2; HR 1.85 95 % CI 1.61–2.12) and high AST (>45 vs. ≤45 IU/L; HR 1.23

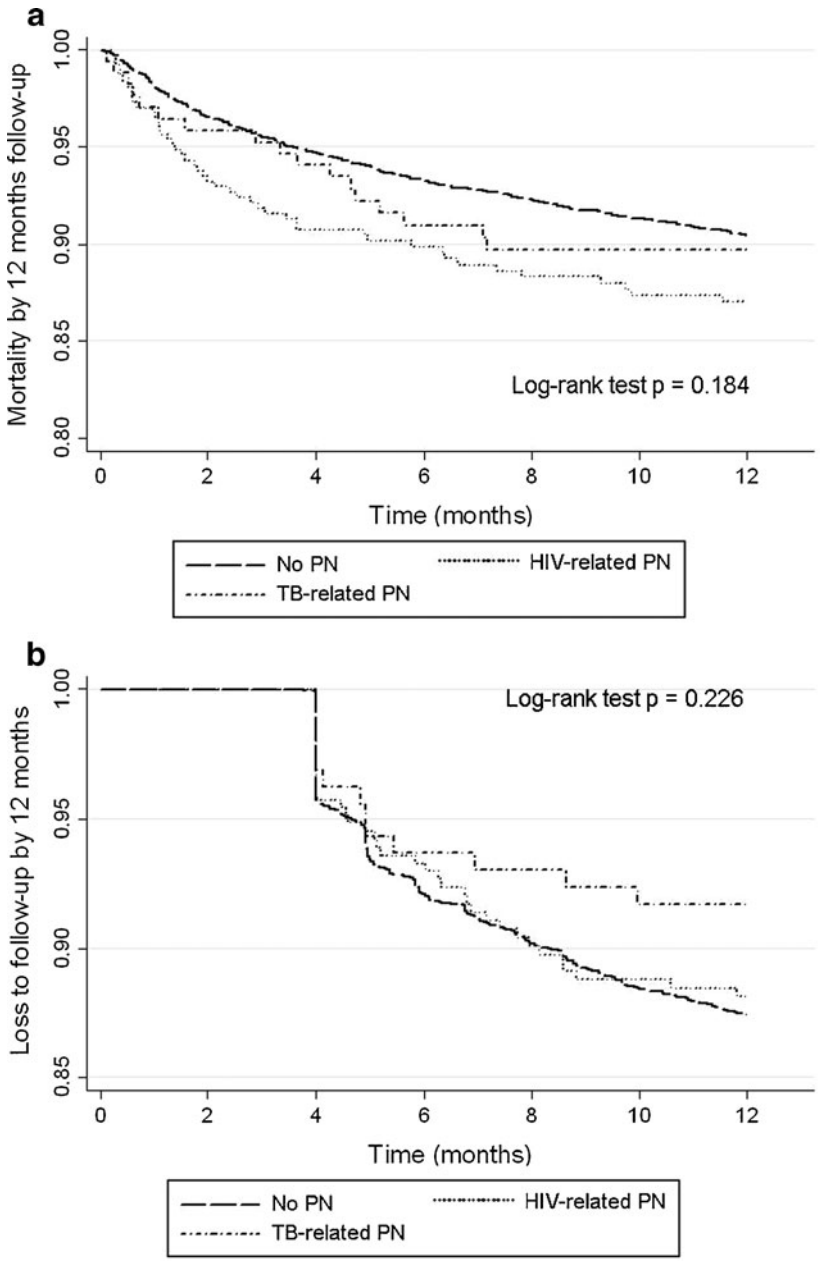

Fig. 1 Crude Kaplan–Meier survival curves of mortality (**a**) and loss to follow-up (**b**) by 12 months post-ART initiation, stratified by no PN, HIV-related PN or TB-related PN. Log-rank test for mortality (**a**) and LTFU (**b**) was p=0.184 and p=0.226, respectively

95 % CI 1.06–1.43) were at increased risk of mortality (Table 2).

Patients with TB-related PN (HR 0.65 95 % CI 0.44–0.97) were less likely to be LTFU during follow-up vs. patients without PN though little effect was noted among the HIV-related PN group (HR 1.02 95 % CI 0.79–1.31) (Table 2). Males (HR 1.25 95 % CI 1.13–1.39), those with low haemoglobin (<10 vs. ≥10 g/dL; HR 1.40 95 % CI 1.25–1.56) and low BMI (<18.5 vs. ≥18. 5 kg/m^2; HR 1.47 95 % CI 1.31–1.64), were at increased risk of LTFU. Younger patients (≤40 vs. >40 years of age; HR 0.89 95 % CI 0.80–0.99) were less likely to be LTFU.

Persistent or recurrent PN

Compared to patients with TB-related PN, patients with HIV-related PN were at increased risk of persistent PN after ART initiation (Table 2). The relation was consistent in sensitivity analyses examining the effect of missing PN stop dates. Two models were constructed: (1) patients with missing stop dates were assumed not to have developed the outcome of interest (not having persistent PN) (HR 1.40 95 % CI 1.07–1.84) and (2) patients with missing stop dates were assumed to have developed the outcome of interest (having persistent PN) (HR 1.34 95 % CI 1.04–1.72). At 6 and 12 months post-ART initiation, there was no difference in the risk of persistent PN between the two groups. At 6 and 12 months, respectively, HIV-related PN patients assumed as not having persistent PN (HR 1.25 95 % CI 0.92–1.69; HR 1.24 95 % CI 0.84–1.82) or as having persistent PN (HR 1.33 95 % CI 0.94–1.88; HR 1.37 95 % CI 0.84–2.25) were not at increased risk of persistent PN compared to TB-related PN. Younger age (≤40 years of age) and high AST (>45 IU/L) were significantly associated with an increased risk of persistent PN at 3, 6 and 12 months post-ART initiation.

Less than 20 % of patients with HIV- or TB-related PN at ART initiation had recurrent PN after ART initiation (Table 2). Patients with HIV-related PN had a similar risk for a recurrent diagnosis of PN (HR 1.28 95 % CI 0.72–2.27) compared to those with TB-related PN. Median time to recurrent PN (accrued from 30 days after recorded stop date of first PN diagnosis) was 7.8 months (IQR 3–15) for patients with HIV-related PN was 7.5 months (IQR 1–18) for patients with TB-related PN. Males (HR 2.11 95 % CI 1.21–3.71) were at increased risk of a recurrent PN diagnosis after ART initiation.

Discussion

Certain peripheral neuropathies may be caused, directly or indirectly, by HIV itself (Singh and Thomas 2010). The likelihood of a particular neurologic syndrome correlates with the clinical stage of HIV infection as reflected by viral load, immune response and CD4 cell count (Singh and Thomas 2010). In the United States, neurologic complications are present in more than 40 % of HIV-positive patients, feature in 10–20 % of patients with AIDS and are prevalent in 80 % of patients on autopsy (Singh and Thomas 2010). The impact in resource-limited setting is not well documented.

We demonstrate that patients with PN at ART initiation present with more advanced HIV disease compared to those without PN. Patients presenting with HIV-related PN at ART initiation may be at increased risk of mortality while paradoxically patients with TB-related PN were less likely to be LTFU when compared to those without PN. We also found that patients with HIV-related PN were more likely to suffer persistence of their PN compared to those with TB-related PN.

Approximately 15–43 % of HIV-infected individuals in the developed world present at clinics with advanced or severe disease (WHO stage III or IV or CD4 ≤200 cells/mm^3) (Nash et al. 2008; Kigozi et al. 2009). Patients that present for initiation of ART with advanced immunosuppression and HIV-associated disease have been shown to be at a higher risk of short-term mortality, are more likely to present with co-morbidities like tuberculosis, have diminished benefits from ART and pose a higher cumulative risk of HIV transmission to others due to a higher viral burden (Kigozi et al. 2009; Mojumdar et al. 2010). Characteristics associated with late presentation in the developed world include older age, male sex, lower income as well as low degree of education (Gonzalez-Duarte et al. 2007; Kigozi et al. 2009; Singh et al. 1996; Gao et al. 2000; Chow et al. 2005). According to the World Health Organization disease stage III or IV classification, approximately 62 % of patients with HIV-related PN and 76 % of patients with TB-related PN can be categorized as late presenters (Kigozi et al. 2009). Consistent with these characteristics, patients with HIV- and TB-related PN in this study presented with features of advanced HIV disease including a lower CD4 cell count, lower haemoglobin, lower BMI and increase in liver transaminases (AST and ALT). HIV-positive women were more likely than men to present with PN (54 vs. 46 %) which is consistent with previous reports on sex differences in PN among patients initiating ART (Mehta et al. 2011).

We showed that patients with PN at ART initiation are most likely to present with advanced HIV disease. In addition, patients with HIV-related PN may be at increased risk of mortality when compared to those without PN. Other significant risk factors for mortality included male sex, age >40 years, low CD4 cell count, low BMI, low haemoglobin and high AST. This is consistent with existing

evidence (Westreich et al. 2009a). Again these factors are typical of late presenters, so patients at a higher risk for mortality, within the first year of initiating ART. The lower BMI, lower haemoglobin and higher AST (consistent with a diet consisting mainly of carbohydrates) suggest a poorer nutritional status and/or underlying nutritional deficiency in patients with PN.

TB treatment does not appear to contribute to or worsen ART treatment outcomes. On the contrary, patients with TB-related PN appear to have better outcomes than those with HIV-related PN. The rate of mortality and LTFU in those with TB-related PN (16.9/100 pys; 21.6/100 pys) was less than those with HIV-related PN (18.6/100 pys; 25.5/100 pys)—a possible explanation for the improved survival may be that those with TB-related PN may have been in care for longer (median 29.2 months [IQR 14.3–44.9] compared to those with HIV-related PN (median 24.6 months [IQR 7.7–40.3]. We demonstrate that TB-related PN patients, who remain in care, are less likely to be LTFU and have a similar risk of mortality compared to those without PN while are less likely to have persistent PN compared to those with HIV-related PN. Adherence to treatment may possibly explain the lower rate of LTFU among those with TB-related PN. Previous work has shown that patients with a history of opportunistic infections are more likely to be adherent to treatment (Singh et al. 1996; Gao et al. 2000), possibly as experience with another illness motivates adherence and healthy behaviour. Patients with TB-related PN were less likely to suffer persistent PN at 3 months post-ART compared to those with HIV-related PN—the removal of TB drugs or completion of TB treatment may resolve PN and reduce the risk among this group. Further, supporting this theory is the finding that the risk of persistent PN disappears at 6 and 12 months post-ART as by this time, patients with TB-related PN are likely to have completed TB treatment and patients in both groups are likely to have demonstrated a response to ART.

Interestingly, ART may reduce the likelihood of neuropathy in HIV-positive patients who present late with PN and advanced HIV disease—even if the ART regimen contains d4T which is known to contribute to ARV-related PN. Less than 20 % of patients with HIV- or TB-related PN at ART initiation had recurrent PN after ART initiation. This is consistent with existing evidence (Lichtenstein et al. 2005; Schifitto et al. 2005). Even though some antiretroviral drugs can cause new or worsen pre-existing peripheral neuropathy, overall, ART has been shown to reduce the likelihood and severity of neuropathy in HIV-positive patients (Lichtenstein et al. 2005; Schifitto et al. 2005). In the developed world, several studies show that initiation of ART is associated with improvement in cognitive and peripheral nervous system function (Robertson et al. 2011). Lichtenstein et al. (2005) showed that although initial use of ddI, d4T, nevirapine or four protease inhibitors was associated with PN, the strength of the association decreased with continued use of all medications studied. Host factors (age >40 years, diabetes mellitus or white race) and signs of increased disease severity (CD4 count 50–199 cells/mm^3 or viral load >10,000 copies/ml) are associated with an increased risk of developing PN during the initial period of exposure to drug therapy (Lichtenstein et al. 2005). Sustained virologic control has been reported to improve peripheral nerve disorders (Gonzalez-Duarte et al. 2007).

These findings should be considered in light of the study limitations. Firstly, the diagnosis of PN may be underestimated in a routine clinical setting. At advanced stages of HIV, larger numbers are more likely to have PN; however, diagnosis of PN was restricted to clinical signs and symptoms in this analysis. While some individuals in this cohort have tests such as nerve conduction studies with laboratory evaluations for vitamin B12 deficiency, diabetes, thyroid disease, and/or connective tissue disorders; however, this is not standard of care in the South African government HIV clinic setting due to limited capacity and resources. Underdiagnosis and therefore misclassification of the exposure in the primary analysis may lead to bias. However, given that we have no reason to suspect that this misclassification would be different between the groups, the estimates that we present would more likely underestimate the true effect.

The prevalence of neurological complications of HIV infection in developing countries is similar to that observed in industrialized countries prior to any antiretroviral therapy among patients with advanced HIV disease (Sacktor 2002). Reports from resource-limited settings suggest a higher prevalence rate of around 11 % (Mehta et al. 2011; Robertson et al. 2011); however, the rate reported here is similar to those previously reported from Johannesburg, South Africa (Westreich et al. 2009a, b).

Secondly, it is difficult to access the impact of other neurotoxic drugs besides ARVs on PN as these were not well documented in the database. The use of pyridoxine (vitamin B6) to prevent INH-induced PN is also not well documented. Thirdly, it is difficult to access the impact of other factors co-existing medical conditions such as diabetes or hepatitis C or certain nutritional deficiencies (vitamin B12 deficiencies) as these were not well documented in the database. Proxies for nutritional deficiency such as low BMI, high MCV (suggestive of alcohol abuse, thyroid disease or vitamin B12 deficiency) and low haemoglobin were included in the analysis so that other conditions causing neuropathy like malnutrition could be excluded. Fourthly, in this cohort, d4T (as part of standard public-sector first-line ART) was widely used (more than 80 % of patients) and this may affect the generalizability of the findings to other settings that have access to different ARV drug regimens.

Lastly, analyses of recurrent and persistent PN are limited by the consistency and accuracy of recording stop dates for PN though results from sensitivity analyses were very similar to those reported. Strengths of this analysis include a large number of patients, the opportunity to comment on associations with prior TB therapy and that the study reflects the clinical diagnosis of PN and ART treatment outcomes in the resource-limited setting which is restricted by the lack of diagnostic neurological testing and which is overwhelmed by the HIV epidemic.

Conclusion

Patients with PN at ART initiation, who present with advanced HIV disease, have higher rates of mortality and lower rates of LTFU compared to those without PN. This reiterates the importance of early identification and initiation of ART—if possible, as WHO recommends at a CD4 cell count less than 350 cells/mm^3 (Walensky et al. 2010; WHO 2010).

Patients with HIV-related PN had increased risk of persistent PN when compared to those with TB-related PN. Removal of TB drugs or completion of TB treatment may contribute to reducing the risk of persistent PN in patients with TB-related PN. Patients with TB-related PN were less likely to be LTFU during follow-up compared to patients without PN. Results support findings that ART reduces the likelihood of neuropathy in HIV- and TB-related PN patients after ART initiation.

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