Prevalence and socio-demographic factors associated with lower-extremity peripheral neuropathy among HIV-infected adult patients on anti-retroviral therapy

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Abstract

This study analysed data from a large cohort of HIV-infected persons to determine the proportion of adult patients who developed peripheral neuropathy (PN) of the lower extremities after initiation on antiretroviral therapy (ART) and further identified the socio-demographic factors associated with the condition. A retrospective cohort study was conducted analysing prospectively collected demographic and clinical data of HIV-infected adults initiated on ART at Parirenyatwa Group of Hospital Family Care Center (PGH-FCC) in Zimbabwe. Participants' data were extracted from an electronic patient management database. A total of 1 546 records were eligible for the retrospective analysis. Most of the data records were from patients between 18 and 81 years. Most records were for females (61.5%), married patients (53.0%), living in the high-density suburbs (52.0%), having reached secondary school (71.7%) and were employed (67.5%). Of the1 546 patient records analysed, 190 (12.3%) HIV-infected patients on ART had a physician-based diagnosis of PN (95% CI=10.8%-14.0%). The most common symptoms reported by patients with PN were sensations of burning type of pain on leg/ feet and paraesthesia. Being divorced (OR=1.66; p=0.001), unemployed (OR=2.86; p<0.01), residing in high density suburbs (OR=1.98; p<0.01), no education (OR=8.21; p=0.014) and having attained primary education (OR=1.92; p=0.014 were all associated with reports of PN. The study findings link the occurrence of PN among HIV-infected persons on ART with advancing age and socio-economic status.

Keywords: Anti-retroviral therapy; associated factors; peripheral neuropathy; prevalence.

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1. Introduction

Despite significant investment towards its treatment, HIV/AIDS is still associated with high morbidity especially in resource-constrained countries such as Zimbabwe. Although the prevalence rates have been dropping over the years, the recent Zimbabwe Demographic and Health Survey (ZDHS) estimated the national HIV prevalence rate at 15%, leaving Zimbabwe as one of the worst affected countries globally (WHO, 2016). Nevertheless, the decline in the HIV prevalence has been attributed largely to expanding disease awareness, positive behaviour change, increased availability and use of anti-retroviral drugs (ARVs) (Joshi et al., 2021). Today, most people living with HIV/AIDS worldwide are living fulfilling lives without activity

limitations and participation restriction because of improved access to adequate treatment (Scanlon and Vreeman, 2013; Pullen et al., 2014; Adem et al.,2019).

With the symptomatology of HIV changing with ARVs, focus is gradually transitioning from acute care to managing chronicity-related concerns (Gonzalez-Duarte et al., 2007; Tumusiime et al., 2014). Moreover, with the holistic biopsychosocial approach directing patient care in many clinical settings worldwide, HIV/AIDS intervention strategies and patient rehabilitation protocols are alert to HIV-associated complications detrimental to health-related quality of life (HRQoL) and functional recovery (Gabbai et al., 2013; Montgomery et al., 2017). Today, peripheral neuropathy (PN) is emerging as one of the most debilitating but under-reported neurological complication associated with HIV infection and antiretroviral therapy (ART) (Esteban et al., 2008; Maritz et al., 2010; Harrison and Smith, 2011; Phillips et al., 2014; Ellis and Latendre, 2016). In a subset of HIV-positive patients, PN may manifest early within the first year of ART initiation and may continue with advancing illness and treatment (Morgello et al., 2004). Generally, little is known about the prevalence of PN in HIV-infected patients on ART in resource-limited settings. The few studies available reported varied prevalence figures. For example, estimates for PN have been reported to be 13% in Malawi (Beadles et al., 2009), 18% in South Africa (Evans et al., 2012), 35% in Ethiopia (Shurie et al., 2010) and 59% in Rwanda (Tumusiime et al., 2014). Similarly, global prevalence rates vary widely from 1.73% to 76% with plethora of contextual factors contributing to occurrence (Parry et al., 1997; Wuff et al., 2000; Simpson et al., 2006; Nicholas et al., 2015; Mkandla et al., 2016). Prevalence rates differ between countries because of different ART guidelines, population differences in diet, nutrition and exercise capacity, socio-cultural and economic differences, use of other neurotoxic medications such as isoniazid, and differing rates of comorbidities (Venkataramana et al., 2005; Chery et al., 2005; Saylor et al., 2017). Hence, the prevalence figures from one country cannot be extrapolated to inform the burden of disease in another country.

In Zimbabwe, the prevalence of PN among HIV-infected people on ART has not been fully investigated. However, one of the first cross-sectional studies published during the peak of the HIV infection documented 44% prevalence with PN diagnosis based on neurological examinations and nerve conduction tests (Parry et al., 1997). Two decades later, with the rate of HIV infection declining, Mkandla et al. (2016) reported a relatively higher cross-sectional prevalence of 59% for moderate to severe HIV-related polyneuropathy established using the Brief Peripheral Neuropathy Screen (BPNS). Although the prevalence estimates may differ between studies conducted in the same country for several reasons such as varied operational definitions of PN, methods of assessment, study designs and sample sizes among other factors, continued surveillance of the condition is still warranted in Zimbabwe against the backdrop of declining HIV infection. The continued monitoring of PN prevalence figures assist in understanding the burden of disease among HIV-infected persons on different regimens of ART and in mapping preventative strategies to minimise the rate of occurrence and progression of the condition.

Plenty of studies have reported the association between PN with a myriad of clinical-related factors such as AIDS, CD4 cell count <100 cells/mm^3, viral load above 10,000 copies/ml, past history of neuropathy, use of other neurotoxic drugs besides ARVs such as isoniazid (INH) for tuberculosis (TB) treatment, nutritional deficiencies (vitamin B_{12} deficiency), history of prior TB infection, coexisting medical conditions such as diabetes, hypertriglyceridemia or hepatitis C and heavy alcohol consumption (Husstedt et al., 2000). However, the relative influence of socio-demographic factors alone on the development of PN among HIV-infected cohort of patients on ART is less explored in the literature and may require further elucidation. Few

studies have documented evidence to the effect that socio-demographic factors such as age, gender, level of education, occupation and place of residence are associated with increased reporting of PN among HIV-infected patients (Tumusiime et al., 2014; Benevides et al., 2017; Adem et al., 2019). Further explorations of this nature contribute to the complete understanding of the epidemiological profile of HIV-infected patients on ART affected with PN regardless of the health or clinical status of the patients.

The greatest concern with PN affecting HIV/AIDS patients is the additional impact it exerts on HRQoL. Clinically, PN progressively presents with distal symmetrical burning sensations, paraesthesia, leg cramps, increased fatigue and lower-limb muscle weakness (Benevides et al., 2017). With advancing illness, the neuromuscular function deteriorates reducing mobility and functional independence, rendering the affected disabled, necessitating the use of assistive devices, causing moderate to severe chronic neuropathic pain, psycho-social problems such as depression and loss of employment (Nicholas et al., 2002; Dudgeon et al., 2004; Ownby and Dune, 2007). Additionally, secondary complications such as muscle contractures, joint stiffness and swelling, poor postural syndromes and back pain may ensue compounding the life of affected persons. The costs placed on HIV-infected patients and caregivers in meeting additional hospital expenses (medical, physiotherapy and pharmacy) related to the PN sequel are tremendous. Altogether, this can contribute to poor adherence to scheduled ART clinic visits and compliance to HIV treatment leading to poor prognosis, increased susceptibility to co-morbidities, and further deterioration in the HRQoL (Mill et al., 2006). Therefore, early identification of HIV-infected patients likely to develop PN becomes important in clinical practice for early monitoring of their quality of life (Haanpaa et al., 2009). Given the possible far-reaching consequences of PN among HIV/AIDS patients and the limited number of studies that have estimated the burden of PN in Zimbabwe, this study analysed data from a large urban cohort of HIV-infected persons to determine the proportion of adult patients who developed PN of the lower extremities after initiation on ART and further identify the socio-demographic factors associated with the condition.

2. Materials and Methods

2.1 Study design and research setting

This survey was part of a broader PERFECT study designed to establish the prevalence of PN among HIV-positive people on ART and further provide evidence on physiotherapeutic interventions commonly used in Zimbabwe for its treatment. To get a snapshot of the 12-month prevalence of PN, a pilot study extracted and analysed prospectively collected demographic, laboratory, and clinical data of a cohort of HIV-infected adults initiated on ART between 1 January 2017 and 31 December 2017 at Parirenyatwa Group of Hospital Family Care Center (PGH-FCC) in Harare, Zimbabwe.

PGH-FCC is the largest hospital-based public ART clinic in Zimbabwe and has been dispensing ARVs since 2004. Harare is the capital city of Zimbabwe, where most of the population resides. For ease of description, residential places in Harare are generally subdivided into high, medium, and low-density suburbs depending on socio-economic status (SES). For HIV/AIDS patients, PGH-FCC provides HIV testing, CD4 cell count monitoring, health care consultation, counselling, and ART medication free of cost. Patients are initiated on ART according to the National Guidelines for ART in Zimbabwe. Briefly, ART-eligible patients are assessed by a physician prior to initiating treatment and put on a first-line regimen depending on clinical status. The patient's demographic, clinical, and laboratory data are

recorded into an electronic patient management database called ePOC (electronic patient online chart). Diagnosis of PN is made by physicians through a standard examination process which includes history taking, symptom review and physical examination. Patients who present with at least one subjective neuropathic symptom (numbness, dysesthesia, burning sensation, stabbing pain) and at least one neuropathic sign (distal weakness, reduced or absent ankle reflexes, abnormal distal vibratory sensation, or abnormal distal pinprick sensation) are usually diagnosed as having PN once other causes were excluded.

2.2 The ePOC database

All patients attending PGH-FCC are captured in the ePOC database as "active" patients (*currently enrolled and attending scheduled visits*) or "visitors" (*circumstantially visited PGH-FCC but are patients for other ART clinics elsewhere*) or "transfers" (*patients who either transferred from other ART clinics or will be transferred to other convenient clinics*). The patient's data are captured under various tabs which include:

(i) Demographics: This tab captures hospital number, patient's name, patient identification number, initiating facility, ethnicity, insurance, telephone, residential address, gender, date of birth, marital status, educational level, nationality, and employment status are all recorded under this tab.
(ii) Visits: For each (un)scheduled visit, this tab captures patient's presenting complaints to the attending doctor, assessment findings, smoking and drinking habits, use of illicit drugs, vital signs recorded, diagnosis made, treatment plan, and prescriptions. In addition, the date, month, and year of the HIV diagnosis and date of ART initiation are also recorded here. Using this tab, it is possible to follow all the subsequent patient's visits made to PGH-FCC from the first visit.
(iii) Diagnosis: This tab gives an overview of all the diagnoses made with dates when the diagnoses were made and the doctor who made the diagnosis. For this study, the main exposure of interest was physician-made diagnosis of PN after the initiation of ART at PGH-FCC. Diagnosis such as hepatitis C virus infection, past or current opportunistic infections, diabetes mellitus, tuberculosis (TB) and others are summarised under this tab.
(iv) Treatment: The tab captures information on the ART and non-ART medication the patient is on and number of weeks the patient has been on that medication. In addition, all the drugs the patient has ever taken are either specifically listed or generally mentioned under the treatment tab.
(v) Laboratory tests: The tab captures results on the most recent and previous laboratory investigations conducted for the patient, including the date for the tests. Investigations such as CD4 count, haemoglobin count, viral load, urea and electrolytes, full blood count are all recorded here.
(vi) Procedures/Investigations: The tab captures additional procedures and imaging investigations conducted for the patient such as X-rays.

2.3 Eligibility criteria

Both male and female medical records of "active" HIV-infected patients aged 18 years and above initiated on ART at PGH-FCC during 2017 and had data prospectively collected for 12-months after initiation were eligible. The records needed to have complete information on socio-demographic variables (*age, gender, education, occupation, employment and marital status*). The first visit to PGH-FCC for each active patient was assessed to ascertain the

presenting symptoms and patient medical history prior to ART initiation. Records of patients with a history of peripheral nerve injury or diagnosis of PN before ART initiation were excluded. Furthermore, clinical pathologies associated with PN were assessed and, with regards to that, eligibility criteria previously used in other studies was adopted (Adem et al., 2019; Chen et al., 2013). Records of patients who developed lower-extremity PN after ART initiation were eligible and those who developed PN prior to having confirmed diagnosis of any of these co-morbidities: TB, disorders of the central nervous system, Vitamin B_{12} deficiency, chronic kidney disease, hypothyroidism, diabetes mellitus, hypertriglyceridemia or hepatitis C were also eligible. Otherwise, HIV-infected patients who had these pathologies co-existing with PN at ART initiation were excluded. The outcome of interest was physician-reported diagnosis of unilateral or bilateral lower-extremity PN explicitly indicated on the ePOC database. The following were used to corroborate the diagnosis from the database: (i) reporting of symptoms such as leg pain, numbness, burning sensation, paraesthesia or dysesthesias, fatigue, muscle cramps, (ii) reporting of signs of distal weakness, reduced or absent ankle reflexes, abnormal distal vibratory sensation, abnormal distal pin-prick sensation, and disturbances in walking, balance and proprioception, (iii) prescription for amitriptyline, and (iv) evidence of dose reduction or complete substitution of the inciting ARV drug after diagnosis of PN.

2.4 Procedure

Institutional permissions were sought from the PGH clinical director and head physician at the PGH-FCC. Subsequently, ethical approval was granted by the Medical Research Council of Zimbabwe (*ref#: MRCZ/A/2339*). A data collection sheet was designed for recording information extracted from the ePOC database. Its design was guided by the study objectives and patient information recorded in the electronic database. After design, the data collection sheet was subjected to two rounds of face and content validation from an expert panel composed of the head physician at PGH-FCC, HIV/AIDS research expert, ePOC data capturing clerk, senior registered general nurse at the PGH-FCC, and two senior members (FM, KM) of the research team working in a supervisory role. The purpose of that validation was to ascertain the relevance of each component question in the data collection sheet and evaluate the overall exhaustiveness of the data collection sheet in eliciting pertinent details.

Subsequently, the instrument was subjected to test-retest reliability evaluation after the content validation. Systematically, the research assistant randomly selected approximately 10% (n=100) of patients' records attended at PGH-FCC between 1 January 2016 and 31 June 2016 and extracted relevant data. Blinded to the repeat procedure initially, the research assistant was instructed to repeat the data extraction process of the same patients' records exactly seven days after completion of the first data extraction. This was to check for reproducibility and agreement of data captured. The seven-day interval is commonly used in literature for the assessment of test-retest reliability of data collection instruments (Bejia et al., 2006). The pre-testing of the instrument also allowed an opportunity for the assessment of the practical feasibility of conducting the study at PGH-FCC and evaluation of intra-rater reliability for the research assistant. Subsequently, main study data collection took place in 2018 and was conducted by a trained research assistant. After that, the collected data was checked for its completeness by the first author and entered in Microsoft excel.

2.5 Data analysis

The data was imported from Microsoft Excel to Statistical Package of Social Sciences (SPSS) version 25.0 for analysis. The Kolmogorov Smirnov and Lilliefors tests were used to check for normality of continuous variables, with parametric or non-parametric tests appropriately utilised thereafter. Descriptive statistics such as mean±standard deviation, median and interquartile range (IQR) and frequencies were used to describe sample socio-demographic and clinical data. The independent student *t*-test compared the mean age of participants by gender with the homogeneity of variance assessed by the Levene's test. Prevalence figures for PN are reported with 95% confidence interval (CI). The Pearson's Chi-square test was applied to evaluate the association between socio-demographic factors and the occurrence of PN. The magnitude of the association between the dependent variable (presence of PN) and the independent demographic variables was indicated by the crude odds ratio (OR) and 95% confidence intervals (CI 95%). Chi-square by linear trend analysis examined for significant increase in the prevalence of PN with increasing age category. One way analysis of variance (ANOVA) compared the mean age by marital and educational status with the Tukey HSD test used for post-hoc analysis. Statistical significance was regarded as $p < 0.05$.

3 Results

3.1 Sample demographics

Table 1: Socio-demographic characteristics of HIV/AIDS patients as captured in the ePOC database at first visit at the PGH-FCC (N=1 546)

Variable	n (%)
Age (years)	
≤20	40 (2.59)
20-29	190 (12.3)
30-39	420 (27.3)
40-49	490 (31.7)
50-59	262 (16.9)
60-69	122 (7.9)
70-79	20 (1.29)
80-89	2 (0.13)
Gender	
Female	951 (61.5)
Male	595 (38.5)
Marital status	
Married	820 (53.0)
Single	431 (27.9)
Widowed	230 (14.9)
Divorced	65 (4.20)
Level of education	
Primary school	172 (11.1)
High school	1108 (71.7)
Tertiary	152 (9.83)
None	114 (7.37)
***Place of residence**	
High density suburbs	804 (52.0)
Middle/Low density suburbs	742 (48.0)
†Employment status	
Unemployed	502 (32.5)
Employed	1044 (67.5)

*place of residence was dichotomised into high and middle/low-density suburbs based on the analysis of the given physical address in the ePOC database; low and middle represented places of residence where people of high socio-economic status and the middle-class lived respectively; †employed represented either formal or informal employment (self-employed) and unemployment meant the patient was not involved in any meaningful occupation generating income for self and family.

Table 1 shows the sample socio-demographic details. A total of 1 546 records were eligible for the retrospective analysis. This figure represented HIV-infected patients who were initiated on ART between 1 January 2017- 31 December 2017 and were seen at PGH-FCC for a period of one year after initiation. Most of the data records were from female patients (61.5%). The mean age of the participants was 42.3±12.0 years and there was significant difference in the mean age by gender [t= -6.18, p<0.001]. Male patients (M=44.6±12.5 years) were significantly older compared to females (M=40.8±11.5). Most records were from HIV-infected patients who were married (53.0%), living in the high-density suburbs (52.0%), having reached secondary school (71.7%) and were involved in meaningful formal or informal employment (67.5%). One way analysis of variance (ANOVA) showed significant difference in the mean age by marital status [F (3, 1542) =248.4, p<0.001]. Post-hoc analysis showed that the divorced and widowed patients were significantly older compared to the single and married. Also, there were significant differences in the mean age by educational status [F (3, 1542) =10.4, p<0.001]. Records showed that patients who had attained none or primary education were significantly older compared to those who reached secondary or tertiary education.

3.2 Clinical variables

Briefly, the median duration of HIV-infection from date of diagnosis to ART initiation at PGH FCC for the sample was 2.1 months (IQR=0.17-4.25 months). There was no significant difference in the rank sum for duration of HIV infection from diagnosis to ART initiation by gender as determined by the Mann-Whitney U test (p=0.20). Most of the HIV-infected patients were on Tenofovir, Lamivudine and Efavirenz as the recommended first-line treatment. The duration of use of ARVs from initiation to the day of PN diagnosis by the PGH-FCC physician ranged between 4-12 months for the sample. Approximately, 70% (n=1 092) of the records of the HIV-infected patients on ART during the study period showed no co-morbid conditions.

3.3 Prevalence of peripheral neuropathy and associated socio-demographic factors

Among the 1 546 patient records analysed, 190 HIV-infected patients on ART had a physician-based diagnosis of PN yielding a one-year retrospective prevalence of 12.3% (95% CI=10.8%-14.0%). The most common symptoms captured were sensations of burning type of pain on leg/ feet and paraesthesia (numbness, tingling). There was no significant difference in the one-year retrospective prevalence of PN by gender [$X^2(1) = 0.25$, p=0.61] (Table 2). Overall, the prevalence significantly increased with advancing age [$X^2_{linear\ trend} = 23.2$, $p=0.002$] especially after the age of 40 years. The age group 20-29 recorded peak prevalence (14.2%) of lower-extremity PN for HIV-infected persons below the age of 40 years. At the time of PN diagnosis, the records for patients with PN showed that they were significantly older (44.6±13.6 years) compared to those without PN (41.9±11.8) as indicated by the *t*-test [$t= -2.92$, $p= 0.04$]. Being divorced (OR=1.66; $p=0.001$), unemployed (OR=2.86; $p\leq0.001$), residing in high density suburbs (OR=1.98; $p=0.001$); no education (OR=8.21; $p=0.014$) and having attained primary education (OR=1.92; $p=0.014$ were all significantly and univariately associated with reports of PN.

Table 2: Factors associated with the report of peripheral neuropathy among 1 546 patients attending the HIV/AIDS clinic at Parirenyatwa Hospital Family Care Clinic

Variable	PN (n=190)	no PN (n=1 356)	OR [95% CI]	p (df)
Gender				0.61(df=1)
Male	70 (11.8)	525 (88.2)	1 (ref)	
Female	120 (12.6)	831 (87.4)	0.92 [0.67-1.26]	
Age (years)				0.002(df=7)
≤20	3 (7.5)	37 (92.5)		
20-29	27 (14.2)	163 (85.7)		
30-39	46 (10.1)	374 (89.9)		
40-49	44 (8.98)	446 (91.0)		
50-59	38 (14.5)	224 (85.5)		
60-69	26 (21.3)	96 (78.7)		
70-79	5 (25.0)	15 (75.0)		
80-89	1 (50.0)	1 (50.0)		
Marital status				0.001(df=3)
Married	96 (11.7)	724 (88.3)	1(ref)	
Single	52 (12.1)	379 (87.9)	0.97 [0.48-1.17]	
Widowed	30 (13.0)	200 (87.0)	1.08 [0.60-2.30]	
Divorced	12 (18.5)	53 (81.9)	1.85 [1.03-3.33]	
Level of education				0.014(df=3)
Secondary	80 (7.22)	1028 (92.8)	1(ref)	
Tertiary	23 (15.1)	129 (84.9)	1.31[0.70-2.20]	
Primary	34 (19.8)	138 (80.2)	1.92[1.10-3.92]	
None	53 (46.5)	61 (53.5)	8.21[2.18-14.8]	
Place of residence				0.001(df=1)
Middle/Low-density	54 (6.72)	750 (93.3)	1 (ref)	
High-density	136 (18.3)	606 (81.7)	1.92 [1.1-2.75]	
Employment status				≤0.001(df=1)
Employed	110 (10.5)	502 (89.5)	1(ref)	
Unemployed	80 (15.9)	1044 (84.1)	2.86[2.01-3.17]	

df =degrees of freedom, OR=crude odds ratio; 95% CI= confidence interval; ref=reference; PN=peripheral neuropathy; p value=significant value for the chi-square test

4. Discussion

The present study established the prevalence of PN and the associated socio-demographic factors among a cohort of HIV-infected Zimbabwean adult patients initiated on ART at PGH-FCC. The data for each patient in the cohort was prospectively followed from the day of ART initiation to a period of one year to determine proportion of patients who developed PN of the lower extremities. With 70% having no co-existing comorbid conditions and duration of ARVs usage minimal, the sample population represented middle-aged HIV positive persons of both sexes. Unfortunately, lower-extremity PN developed in one out of ten of these HIV-infected patients who were initiated on different regimens of ART. Characteristically, patients with HIV-related PN were males or females of older age residing in the high-density suburbs, mainly divorced, unemployed, and reporting low levels of education. Discounting the reported significance of the patient health and clinical status, the present study findings on socio-demographic factors associated with PN potentially suggests a complex interaction of the person's socio-economic status in the occurrence of PN among HIV-infected people attending the ART clinic at PGH-FCC.

Although the prevalence rate found in the present study was relatively low, the estimate agrees with figures reported from other African studies using similar methodological designs. Beadles et al. (2009) undertook a similar retrospective analysis of secondary data gathered from one major urban public ART clinic in Malawi which relied on clinician-made diagnosis of PN. Despite analysing data for the first quarter of 2006 and using a relatively large cohort of 3 341 HIV-infected adult patients receiving ARVs compared to the present study, Beadles et al. (2009) reported a consistent prevalence of 13% (n=428) for PN. However, details about period of HIV-infection and duration on ART for the sample population were not highlighted in the latter study for a comparative analysis with the current study. Nevertheless, these findings confirm that retrospective cohort studies with a relatively shorter follow-up period (3-12 months) generate modest prevalence rates. In another context, Evans et al. (2012) utilised a similar design and found that 18.3% of 9 399 HIV-infected adult (median age=37.7 years) patients attending a local ART clinic in South Africa developed PN, diagnosed through standard examination, after ART initiation between June 2004 to June 2009. The higher prevalence for the latter study compared to the present study could be attributable to the differences in the follow-up time (one year *vs.* five years). Altogether these findings potentially

indicate heightening prevalence of PN with increasing duration with HIV infection and concomitant increase in length of exposure to ARVs from initiation. There is evidence linking duration of HIV infection and duration on ART to the occurrence of PN (Evans et al., 2011; Menezes et al., 2011). It is plausible that the 12.3% prevalence established for the Zimbabwean cohort of HIV-infected adult patient on ART from PGH-FCC reflects the relatively shorter duration of the HIV-infection from date of diagnosis to ART initiation and the length of ART exposure among other clinical-related factors.

Large variations in the prevalence figures between studies emanate from innumerable factors such as differences in operational case definition of PN, method of assessment and diagnosis, study design-related differences (*cross-sectional vs. retrospective vs prospective*), target population differences in clinical and immunological data (*HIV+ patients ART naïve vs. HIV+ patients on ART; CD4 cell and viral load count at the time of PN diagnosis; duration of HIV-infection; duration of ART usage; presence or absence of comorbidities*) (Cherry et al., 2005; Venkataramana, et al., 2005). Cross-sectional and prospective cohort studies report higher prevalence figures compared to retrospective cohort studies. Shurie and Deribew (2010) reported a relatively moderate cross-sectional prevalence of 34.6% among 2 417 Ethiopians with HIV infection. Another cross-sectional study conducted among 507 women and men on ART aged between 18 and 60 years randomly selected from eight selected clinics in Rwanda showed a relatively higher prevalence of 59% for PN of the lower extremities based on the validated BPNS (Tumusiime et al., 2014). In addition, neuropathy rates may differ between countries because of different ART guidelines, population differences in diet, nutrition and exercise capacity, use of other neurotoxic medications such as isoniazid, and differing rates of comorbidities (Saylor et al.,2017). In Gabon, in a cross-sectional observational study conducted at the University Teaching Hospital in 2014 involving 620 adult HIV patients attending the hospital ART clinic, the odds of having PN increased with the use of D4T ART options [OR=2.6; 95%CI: 1.4-4.6], presence of opportunistic infections [OR=3.8; 95%CI: 2.2-6.7], and exposure to isoniazid [OR=1.9; 95%CI: 1.3-3.0] (Kouna-Ndouongo et al., 2015). Without controlling for possible clinical confounding variables, the current study showed that the prevalence of PN among HIV-infected persons on ART significantly increased with advancing age. This finding potentially suggests that PN becomes increasingly common with age among HIV-infected people on ART. Although this finding has also been reported in previous studies, the explanation for the association is unclear from the current study. Literature links the association between age and HIV-related PN to factors such as increased longevity on ART, duration of HIV infection, stage of HIV disease, presence of opportunistic infections, and deteriorating peripheral nervous system among other factors (Mehta et al., 2011) However, given the relatively short duration of HIV infection and ART exposure reported for the sample population in the current study, other factors may possibly explain the increase in neuropathy rates with age. Of note, the age group 20-29 years recorded the peak prevalence of 14.2% for patients below 40 years necessitating the need to monitor the occurrence and progression of the condition from this age group henceforth. Some studies identified higher age (>40 years) to be a significant predictor for developing HIV-related PN (Chen et al., 2013; Pullen et al., 2014; Kouna-Ndouongo et al., 2015).

Despite male patients being significantly older compared to females, the current study showed no significant difference in the prevalence of PN by gender. This finding indicates that both male and female HIV-infected adult patients on ART were equally affected, possibly dismissing the relative influence of gender or the biological differences between the sexes in the occurrence of PN. Although other studies report consistent findings with the current study despite differences in study designs (Chen et al., 2013; Pullen et al., 2014; Kouna-Ndouongo

et al., 2015) others reported conflicting findings (Wuff et al., 2000; Evans et al., 2012). Evans et al. (2012) found that women were more likely to develop PN compared to men. However, the latter study included HIV positive patients who had not received ART compared to the present study which had HIV-infected persons on ART. For the present study, the basis for lack of a significant statistical association between gender and PN is unclear. Although further studies are needed to elaborate on these findings, it suffices to recommend for monitoring of all HIV-infected persons on ART regardless of gender for the symptoms of PN.

This study indicated a higher prevalence of PN in HIV positive people on ART living in high-density suburbs. These findings illustrate the importance of place of residence in the development of HIV-related PN of the lower extremities when on ART. The reasons for this association are unclear but could be informed by the lifestyles differences between people living in high and low-density suburbs. Although no study has directly compared the prevalence of PN by place of residence as was done in the current study, Tumusiime et al. (2014) compared urban and rural dwellers in Rwanda. The urban residents with HIV showed greater propensity for PN than rural counterparts. The authors linked the high prevalence among urban dwellers to physical inactivity given plethora of evidence to the effect that physical activity offer protective effect to rapid development of neurological symptoms among HIV positive patients on ART (Schuelter-Trevisol et al., 2012; Franz and Murenzi, 2013).

Among HIV-infected patients on ART, the current study also showed that being unemployed, divorced and uneducated significantly increased the odds of reporting PN. These findings have been reported with conflicting evidence in literature and the reasons for the associations are unclear from the present study. Tumusiime et al. (2014) found a significantly higher prevalence (72%) for PN among unemployed HIV positive patients compared to HIV positive self-employed (63%) or peasants/farmers (47%). In contrast, HIV positive “active workers” were reported to have a significantly higher prevalence of PN (34.9%) compared to unemployed HIV patients (24.0%) in Gabon (Kouna-Ndouongo et al., 2015). Altogether, these findings highlight the importance of socio-cultural context in determining the relative impact of employment status in the occurrence of PN among black HIV-infected people in Africa. In addition, these findings shows that the relative influence of socio-economic status in PN occurrence is highly context specific.

Tumusiime et al. (2014) also found that marital status was significantly associated with reporting of PN ($p=0.003$). In that study, being divorced/separated increased the risk of developing PN three-fold than being single. These findings were consistent with the present study findings. However, the reason for this association is unclear. Nonetheless, it is possible that a combination of factors such as patient’s demographic, health, and quality of life status among other factors could explain the high neuropathy rates among divorced HIV-infected patients on ART. For the current study, post-hoc analysis showed that the divorced patients were significantly older compared to the single and married patients but not the widowed. However, the significant difference in the prevalence figures between the divorced (18.5%) and widowed (13.0%) dismisses the relative influence of increasing age in explaining the association and could possibly indicate the importance of other factors. Future studies may aim to verify the early occurrence of neurological symptoms among HIV-infected patients on ART by marital status and the possible connection with other biopsychosocial factors.

Low educational status was also associated with lower-extremity PN in the present study. Predominantly, HIV-infected on ART who had none, or primary level of education had increased odds of reporting PN. These findings were, however, in disagreement with the findings of Tumusiime et al. (2014) who reported significantly higher prevalence of PN for HIV patients on ART with higher level of education ($p=0.01$) in Rwanda. In Gabon, the level

of education was found to have no effect on the occurrence of PN among adult HIV-infected people regardless of ART (Kouna-Ndouongo et al., 2015). These conflicting results possibly reflect differences in the sample population and lifestyles between countries. From the current study, it is unclear how educational status contributes to the development of PN. Further studies are needed to ascertain the link between educational status and development of PN controlling for other important clinical and demographic variables such as duration of HIV infection, ART exposure, HAART option, CD4 and viral load count, employment and marital status.

4.1 Limitations of the study

This is the first study to determine the prevalence of lower-extremity PN among HIV-infected patients on ART and the associated socio-demographic factors from Zimbabwe. However, this study had limitations; and the results should be interpreted cautiously cognisant of these limitations. Although the research setting was a large referral public hospital with the largest ART clinic and widest catchment area in Zimbabwe, the study involved secondary data analysis of patient electronic records from one hospital known for servicing mainly Harare residents. This limits the generalisability of the study results to other public, municipal and private ART clinics because of selection bias. Future studies may aim to improve on the design of the study and adopt robust prospective cohort studies incorporating a random selection of ART clinics in Harare, Zimbabwe to improve on the external validity of the results. In addition, the study design was limited to retrospective data analysis of HIV-infected patients initiated on ART solely in 2017 and followed for a period of one year to determine proportion of patients who developed lower-extremity PN based on clinician-made diagnosis. This relatively short follow-up period and over-reliance on physician diagnosis without further laboratory or electrophysiological tests could have under-estimated the burden of the condition especially considering its possible association with advancing illness. Additionally, the study only investigated for PN of the lower-extremities and excluded upper-limb complaints. Although this study univariately determined socio-demographic factors associated with PN, there are other important predictor variables that could explain the occurrence of the outcome variable that were not investigated in the study or should have been included in binary or multinomial logistic regression to fully understand their influence. Factors such as baseline and recent CD4 and viral load count, duration since HIV diagnosis, ARV started with, ARVs current regime, ARVs regimen changes, stage of disease and opportunistic infections. Future papers should establish the association between the patient's health and clinical status and the development of PN separately.

5. Conclusions

PN is common among HIV-infected adult patients on ART attending PGH-FCC. PN patients are more likely to be older, divorced, unemployed, uneducated and of both sexes. Cognisant of study limitations, these main findings link the occurrence of PN among HIV-infected persons on ART with advancing age and patient SES (employment, place of residence, educational status). However, future studies could investigate the impact of health and clinical status in combination with demographic factors to fully understand the explanatory variables for the occurrence of lower-extremity PN among HIV-infected adult patients.

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