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Original Article

Risk factors for peripheral neuropathy in HIV patients: A systematic review

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Abstract

Aim: Neurologic complication is the most complication of HIV infection, peripheral neuropathy, specifically with about 30-67% of HIV patients experiencing this condition. Distal sensory peripheral neuropathies (DSP) associated with severe pain and lack of a patient's quality of life, and it has been documented to have up to 60% in advanced HIV prevalence. Other factors such as older ages, alcohol use, anti-tuberculosis drugs, low cell count of CD4+, deficiency of some nutrition, women, and high plasma viral load are announced as risk factors for PN in early publication.

To perform a systematic review to identify risk factors estimates of peripheral neuropathy among HIV-infected adult patients.

Material and Methods: We use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist in this review. A search to review articles was performed in PubMed, MEDLINE, PROQUEST, EMBASE, and Google Scholar that were published from January 2014 to December 2018. We approved the latest five years of publications. Study titles were first screened, then second selection by title and abstract reviews. For the third and last selection, we tested those full text, then applied eligibility criteria.

Results: We found 17795 citations, and at the end, four publications included. We found that age is a high-risk factor for peripheral neuropathy in HIV-patients, perhaps due to the increased risk of polyneuropathy as a consequence of oxidative stress and less efficient peripheral nerve regeneration among older people. Female was more likely to develop PN, although only one study confirmed this according to our analysis. Besides, PN was found higher among individuals who had previous CART use but later discontinued, thereby increasing the risk of PN. Of note, individuals with detectable viral load at entry had more probability of new DSP.

Conclusion: Age, female sex, CART discontinuation, and initially, detectable viral load were at an increased risk of suffering from peripheral neuropathy in HIV-patients.

Keywords: HIV, peripheral neuropathy, neuropathy, risk factor, systematic review, ART.

INTRODUCTION

Human Immunodeficiency Virus (HIV) INFECTION AFFECTS ABOUT 35.2 million people world-wide (1). Neurologic complication is the most complication of HIV infection, peripheral neuropathy specifically (2) with about 30-67% of HIV patients experiencing this condition (3). HIV associated sensory neuropathy (HIV-SN) can be devided into distal sensory peripheral neuropathies (DSP) and antiretroviral toxic neuropathies (ATN) (4). DSP is uncommon in the early stages of HIV infection. Thirty percents of hospitalized patients world-wide with advanced stage of HIV has been reported to have DSP before the highly active antiretroviral therapy (HAART) era (5). DSP associated with severe pain and lack of patient's quality of life and it has been documented to have up to 60% in advanced HIV prevalence (6).

Since the use of antiretroviral therapy (ART) era, the incidence and prevalence of HIV-SN has been increased (7). Regarding ART toxicity of the "d-drugs", these medications should be avoided in patients at high risk for DSP. Mechanisms of this condition are unknown, with some evidence implicating gp120 mediated neuronal apoptosis for viral-induced DSP and mitochondrial toxicity, in dideoxynucleoside toxicity-induced DSP (8).

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The combination antiretroviral therapy (c-ART) has decreased the incidence of HIV-SN, but DSP remains problematic (9).

However, either HIV or PN effect associated ART can coexist and maybe difficult to distinguish them symptomatically (10). Other factors such as older ages, alcohol uses, anti-tuberculosis drugs, low cell count of CD4+, deficiency of some nutrition, women, and high plasma viral load are announced as risk factors for PN in early publication (11).

The purpose of this review is to perform a systematic review to identify risk factors estimates of peripheral neuropathy among HIV-infected adult patients.

MATERIAL and METHODS

We use PRISMA statement and checklist in this review (12). A search to review articles was performed in the following search engines: PubMed, MEDLINE, PROQUEST, EMBASE, and Google Scholar that were published from January 2014 to December 2018. We approved the latest 5 years publications because Ghost S et al. has been made a systematic review that made in year 2012 and included all of publications before year 2012. Ethical approval for this review was not required. A comprehensive search for PubMed formulated as including of three sections: 1. 'Peripheral Neuropathy' [PN]; AND 2. 'HIV' AND 3. 'Risk factor'. For EMBASE, MEDLINE, PROQUEST, and Google Scholar we used section 1 combined with section 2 as search considered by peer-reviewed papers. Study titles were first screened on, then we screened second selection by title and abstract reviews. For third and last selection we screened those full text, then applied eligibility criteria, with main priority on measured the quality of statistical analyses and the outcome.

Key domains were study design and objective, population, measure of instrument, report of data and data analysis. Fourteen criteria were identified. Table 2 presents criteria and scores. Term (1) showed that the item was well described and/or well performed. Term (0) showed that the item was has not been reported or unclear or has not been well performed.

Table 1. Eligibility criteria in PICOS model

	Inclusion	Exclusion
Populations	Adult (>18 years old) with HIV	Children Not human Just women population or just men population
Intervention	Objective to investigate risk factors of peripheral neuropathy associated HIV	Studies with purpose only to know peripheral neuropathy prevalence
Control (only applicable in case-control design)	Healthy adult or HIV-negative adult	
Outcomes	Peripheral neuropathy as measured by certain method of assessment	Besides peripheral neuropathy
Study Design	Cohort Case-control Cross-sectional	Case studies Qualitative research Review Randomized controlled trial
Language	English	
Statistic	An adequate method of statistical to elaborate or evaluate risk factors. Present adequate measure of association (i.e. OR/RR with 95% CI or present adequate data to cumulative OR/ RR)	Just only descriptive statistics Only use correlations or simple t-tests to compare 2 groups.

OR, Odd Ratio; RR, Relative Ratio; CI, Confidence Interval

Extracted items were characteristic of the participants, demographic, instrument study design, definition of the outcome, and analysis Determinants were factors that related to health and socio-demographic. The odds ratio (OR) was a principle summary measure with corresponding 95% confidence interval (CI). When odds ratio was unclear, p value was presented. (Table 1)

RESULTS

We found 17795 citations. At the first screening, we removed the duplicate publications and 17703 publications remained. Then, on the second screening that title-based and abstract-based (eligibility of criteria used), 76 publications remained. Most publications were excluded because of not analytical epidemiological study and PN not an outcome. On a third screening, after full text reviewed, 72 papers were excluded. Finally, we included 4 publications. More detailed is provided Figure 1.

Table 2 described the results of methodological quality assessment. Methodological quality was high. The case-control study scored was 11. Median total quality score per item was 11. Quality of statistical analyses was moderate (3/4 appropriate publications controlled for confounding or effect modification, 4/4 publications described the statistical model used appropriately,). Items that have

a score below the median (from highest to lowest) were appropriate definition and assessment of determinants, the measurements of most important outcome, other sources of bias, participation rate, and others' score were 4. Study characteristics are presented in Table 3 and participant characteristics are presented in Table 4.

Table 2. Results for methodological quality assessment

	Tumusiime et al., 2014	Malvar et al., 2015	Ekenze et al., 2014	Kimuwa et al., 2014	Total quality score pert item
Study design and objective					
1. objective of the study was clear	1	1	1	1	**4**
Study population					
2. Description of eligibility criteria	1	1	1	1	**4**
3. Description of selection of study population	1	1	1	1	**4**
4. Description of population characteristics	1	1	1	1	**4**
5. Case–control: definition of cases and control were mentioned	-	-	1	-	**1**
6.Participation rate is more than 80%	0	0	0	0	**0**
Measure of instruments					
7. Appropriate definition and assessment of outcome	1	1	1	1	**4**
8. Appropriate definition and assessment of determinants	1	1	0	1	**3**
Data					
9. The measurements of most important outcome	1	1	1	1	**4**
10. Frequencies of most important determinants	1	1	0	1	**3**
11. Measures of association presented	1	1	1	1	**4**
Analysis					
12. Appropriate statistical model	1	1	1	1	**4**
13. Controlled for confounding or effect modification	1	0	1	1	**3**
Other					
14. No identification of funding sources and conflicts of interest	1	0	1	1	**3**
15. Other sources of bias (that not mention)	0	0	0	0	**0**
Total score for each study	**12**	**10**	**11**	**11**	

1, and/or well performed; 0, has not been reported, has not been well performed or unclear; -, not have been applicable yet

There were 4 studies conducted in USA, Uganda and Zimbabwe, Rwanda and Nigeria. One of four publications that selected in this review was cross-sectional. Two cohort publications had follow-up a year and 7 year, and another was case control. The sample size ranged from 300 to 2895 patients. All studies concerned DSP. Methods used to assess DSP included sign and symptom in one study, medical record form in one study, and the Brief Peripheral Neuropathy Screen (BPNS instrument in 2 studies (13-16). The valid assessment for DSP is BPNS, we can assess DSP by asking participants to rate sign and symptom for each leg, elaborated by score of 1 (mild) to 10 (severe). Symptoms like burn, pain, and aching in both leg or both foot, needles and pins in both leg and/or both foot and numbness in boot leg and/or both feet. The result in the BPNS was perception loss of vibration. It is evaluated by a 128-Hz tuning fork, struck maximum then applied to the distal interphalangeal joint of the hallux on both foot, each. Abnormal ankle deep tendon reflexes were defined with hyperactive, normal, hypoactive, absent or clonus.

Three of four papers presented multivariate results (13, 15, 16) and only one paper univariate result (14). Outcome was described as peripheral neuropathy.

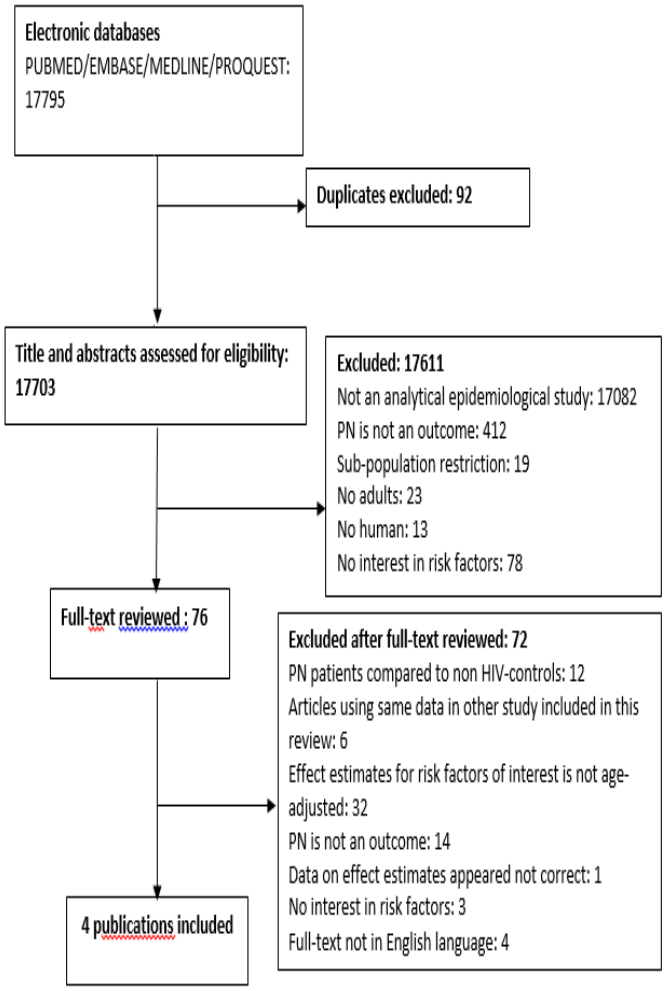

Figure 1. Flow diagram. The stages of study selection for systematic review

Results by subgroups

Demographics

Effect of age as a determinant for peripheral neuropathy has been examined (13-16). In univariate analysis in the case-control study, age has been found as a low

association with peripheral neuropathy because the age of all the participant was younger than 40 years, yet it was concluded that older age was not have a strong related to PN (14). In multivariate analyses, age effect was found. (13, 15, 16).

Malvar et el. was found that men were more likely to experience peripheral neuropathy compared with women (OR 0.47, 95% CI 0.22-0.989). Tumusiime et al. found that PN has a strong related with higher level of education, duration on ART, and the urban vs. rural setting.

Health related factors

Ekenze et al. found that Hb, duration using HAART, and height were associated with PN as an independent factor. Hb is the strong determinant based on this study. Participants with low Hb have 7.4 times the incidence of having PN. Different with other, it was said that pre-ART

Table 3. Study Characteristic
Cross sectional

First author	Country, year of study	Population	Size of population	Neuropathy type	Mean (SD) age (on year)	Patients with PN (%)	Assessments of HIV	Definition & methods of identifying PN	Method of identifying risk factors	Risk factors mentioned	Statistical analysis
Kimuwa et al.	Uganda and Zimbabwe, Sept 2003 – Oct 2004	HIV-infected patients ART-naïve; age >18years old with CD4+ cell count less than 200cells/uL. All patients saw a doctor routinely in weeks 4, 12, and then every 12 weeks.	2895	DSP	Not available	290 (11%)	Routinely blood examination and clinical assessment; cell count of CD4 less than 200 cells/uL; ART users.	Sign and symptom. Grade 1: not requiring treatment. Grade 2: requiring analgesic. Grade 3: requiring a narcotic. Grade 4: despite narcotics.	Structured questionnaire each scheduled 4-weekly clinical visit	Gender, age, HIV WHO stage, pre-ART CD4+ cell count, pre-ART weight, current CD4+ cell count, currently on stavudine, currently on isoniazid, isoniazid with/ without pyridoxine, currently on didanosine, pre-ART height	The Kaplan-Meier method with Cox models

ART, Anti Retroviral Therapy; PN, Peripheral Neuropathy; DSP, Distal Sensory Polineuropathy.

Table 3. Study Characteristic (continued)
Cohort

First author	Country, year of study	Definition of population	Size of population	Neuropathy type	Mean (SD) age (on year)	Patients with PN (%)	Assessments of HIV	Definition & methods of identifying PN	Method of identifying risk factors	Risk factors mentioned	Statistical analysis
Malvar et al.	USA, Sept 4, 2003 – Jan 14, 2010	HIV-infected patients; age > 18 years old	493	DSP	42.4 (8.6)	131 (26,6%)	plasma VL <50 copies/ mL and cell count of CD4 level measured	BPNS	Interview	Age, gender, ethnicity, height, c-ART use, d-drug use, CD4 nadir, CD4 current, plasma VL, HCV seropositive, diabetes, triglycerides lifetime substance use disorder, alcohol, methamphetamine, cocaine, opioids	Logistic regression models
Tumusiime et al.	Rwanda, 2011	HIV-infected patients, ART users; age >18 years old	507	DSP	No PN 37 (8.8); with PN 42 (9.2)	300 (59.2%)	Medical files: patients who are ART users and have CD4+ count less than 350 cells/uL		Interview and medical records	Age, education, occupation, marital status, setting/residence, CD4 cell count, duration since HIV diagnosis, current ART regiment, duration on ARTs, ART regimen changes, ART started with/ without D4T.	Logistic regression analysis

VL, Viral Load; ART, Anti Retroviral Therapy; PN, Peripheral Neuropathy; DSP, Distal Sensory Polyneuropathy; BPNS, Brief Peripheral Neuropathy Screen.

Table 3. Study Characteristic (continued)
Case control

First author	Country, year of study	Base population	Case and controls	Neuropathy type	Study size	Mean (SD) age (on year)	Patients with PN, n (%)	Methods of identifying HIV	Definition & methods of identifying PN	Method of identifying risk factors	Risk factors mentioned	Statistical analysis
Ekenze et al.	Nigeria, Jan-June 2007	HIV-infected patient (naïve and on HAART patient, selected by systematic random sampling	Cases: patients developing PN. Controls: match on sex and age HIV-negative adults	DSP	100 HAART naïve, 100 HAART users, 100 controls	Cases: HAART naïve 36 (30-40), HAART users 33 (30-40) Controls: 38.5 (32-50)	HAART naïve 37 (37%), HAART users 48 (48%)	ELISA	BPNS	Not mention	Age, height, BMI, hemoglobin (Hb), duration on HAART, modified NIS, CD4 cell count	Logistic regression analysis

HAART, Highly Active Antiretroviral Therapy; ART, Anti Retroviral Therapy; PN, Peripheral Neuropathy; DSP, Distal Sensory Polyneuropathy; BPNS, Brief Peripheral Neuropathy Screen; ELISA, enzyme-linked immunosorbent assay; BMI, Body Mass Index.

Table 4. Risk factors for peripheral neuropathy according to the 4 publications included

Risk factor category	First au-thor	Variables	Definition of the risk factor	Effect size	Confidence interval	P value	Measure of effect size
Demographic characteristic	Malvar et al.	Age	Age per year	1.051	1.013-1.091	0.0078	OR
		Gender	Men	0.47	0.22-0.989	0.048	OR
	Tumusiime et al.	cART use at study entry	Current	3.34	1.41-7.89	0.00043	OR
			Past	9.02	2.90-28.04		
	Kimuwa et al.	Lifetime history of any substance abuse /dependence	Yes	2.13	1.033-4.41	0.036	OR
			Opioid: history of Ab/Dep	2.87	1.31-6.28	0.008	OR
		Age	Age 42(SD ±9.2)	1.1	1.0-1.1	<0.001	aOR
		Education	Primary	0.6	0.3-1.0	0.04	aOR
		Setting/residence	Rural	0.1	0.06-0.3	<0.001	aOR
		Age	Per 10 years older	1.29	1.12-1.49	<0.001	aHR
Health status	Ekenze et al.	Height	Height (< or ≥1. 7m)	0.122	0.025-0.601	0.010	OR
		Hb	Hb (< or ≥10g/dL)	7.474	1.782-31.339	0.006	OR
		HAART duration	Duration < or ≥12 months	0.228	0.069-0.756	0.016	OR
	Kimuwa et al.	Pre-ART weight	Per 5 kg heavier	1.07	1.01-1.13	0.001	aHR
		Current stavudine use: yes vs. no		4.16	3.06-5.66	<0.001	aHR
		Isoniazid without pyridoxine		1.67	1.02-2.71	0.04	aHR
		Current didanosine use: yes vs. no		1.60	1.19-2.14	0.002	aHR
	Tumusiime et al.	Duration on ART	1-3 years	2.6	1.4-4.8	0.001	aOR

ART, Anti Retroviral Therapy; OR, Odds Ratio; aOR, adjusted Odds Ratio; aHR, adjusted Hazard Ratio; Hb, Hemoglobin

height, currently stavudine users, isoniazid users without pyridoxine, and didanosine users played a role as a strong risk factor to PN based on Kimuwa et al. study. Tumusiime et al. said that there is a strong association between duration on ART (after 1-3years) and incidence of PN.

DISCUSSION

In this systematic review we have tried to identify and summarize risk factors estimates of peripheral neuropathy among HIV-infected adult patients. We found that age is a high-risk factor for peripheral neuropathy in HIV-patients. Further discussion for this statement based on early studies who said that the role of age is still unknown, but that is thought that older age can make the peripheral nervous system turns to polyneuropathy. (17-18) A long peripheral nerves, large, metabolically stressed are more dangerous to toxicity and damage (9). Older age makes that pathology gradually worse and that subclinical damaging nerve may be happen in people with HIV who are asymptomatic for DSP and only manifest with advancing age (14).

Previous study found that female sex was 10 times sensitively to develop PN in the first year of ART in a Kenyan cohort (sixty three percents initiating stavudine regimens), the explaination of this statement is that women has a more courage and insist to report their symptom compared with men (17). Currier et al. said that female more often to discontinued ART, they complain about the

adverse events such as PN more often compared with men (19). In our systematic review we found the association between incidence of PN and gender only in Malvar et al.

The small group of individuals (n=50), who had previous CART use but discontinued then, have been declared to be the highest prevalence of PN. This group has a history of advanced immunosuppression stage than ART-naïve participants. Among ART-naïve, rates of new DSP were low compare with those of small group. Also, individuals with detectable viral load at entry had more probability on new DSP (20).

Low count of haemoglobin (Hb) was a significant risk factor for PN (21). Nutritional deficiencies play a role of the pathomechanism, firstly from malabsorption, vitamin B12 and folate deficiencies, though these were not assessed in this review. Anaemia could also occur from enhanced cellular immune activation, then lowering erythropoietin and infiltration on the bone marrow precursor cells (22).

The incidence of PN became a low rates in the general HIV-patients, because the WHO recommendation declared that stavudine regiment is no longer known as a first-line subtitution in the latest guideline, nor is didanosine regiment mentioned in the second line (1).

However, there is some limitation of this review. First, studies that include in this review were small (four studies in total) despite of the extensive literature search. Second, there were different modality and criteria for diagnose peripheral neuropathy in each included studies, so there might be over and under diagnoses in each cases.

There were some restrictions of publication applied as the strength poin of this review. The last systematic review about the risk factor related peripheral neuropathy in HIV patients was made in 2012, so by this review hopefully we can refresh and update information about the related topic.

CONCLUSION

Age, female sex, CART discontinuation, and initially detectable viral load were at an increased risk of suffering from peripheral neuropathy in HIV-patients.

Competing interests: The authors declare that they have no competing interest. .
Financial Disclosure: There are no financial supports
Ethical approval: Ethical approval for this review was not required. A comprehensive search for PubMed formulated as including of three sections: 1. 'Peripheral Neuropathy' [PN]; AND 2. 'HIV' AND 3. 'Risk factor'. For EMBASE, MEDLINE, PROQUEST, and Google Scholar we used section 1 combined with section 2 as search considered by peer-reviewed papers.

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