

Original Research Article

Peripheral neuropathy in people living with human immunodeficiency virus and acquired immunodeficiency syndrome on antiretroviral therapy

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ABSTRACT

Background: Peripheral neuropathy is a common neurological complication in people with human immunodeficiency virus (HIV) infection. HIV-associated sensory neuropathy (HIV-SN) is defined as the presence of neuropathic symptoms and at least an abnormal perception of vibrations of a 128 Hz tuning fork on the great toe or abnormal ankle reflexes or both. Brief peripheral neuropathy screening (BPNS) tool is employed in identifying HIV-SN based on a directed symptom questionnaire and limited clinical examination. The present study was conducted to determine the prevalence and drug regimens related to peripheral neuropathy in people living with HIV and Acquired immunodeficiency syndrome (AIDS) on antiretroviral therapy (ART) so as to help improve the care for those on ART. The objective was to study the prevalence of peripheral neuropathy in people living with HIV and AIDS on ART using AIDS clinical trials group validated BPNS tools.

Methods: Cross-sectional study on 198 HIV-seropositive cases aged above 18 years on ART attending centre of excellence (CoE) ART centre, RIMS Imphal. The presence of peripheral neuropathy was examined by using a BPNS among the participants.

Results: Peripheral neuropathy was found in 46 (23.2%) out of 198 participants using BPNS. In this study a positive association between the duration of treatment with ART and use of protease inhibitor regimens with the development of peripheral neuropathy was significant.

Conclusions: Peripheral neuropathy in patient with HIV and AIDS on ART had significant association with duration of treatment with ART and use of protease inhibitor combination in the ART regime.

Keywords: Peripheral neuropathy, ART, Duration, Protease inhibitor

INTRODUCTION

HIV-associated distal sensory polyneuropathy is the commonest peripheral neuropathy in HIV infection and in those on ART. With introduction of highly active antiretroviral therapy (HAART) in 1996, HIV infection associated complications of central nervous system have declined. However, the incidence and prevalence of peripheral nervous system complications of HIV infection

remains high. HIV envelope protein gp120 causes neuronal injury through perineuronal Schwann cells. This may eventually induce upregulation of tumor necrosis factor-alpha resulting in apoptotic death of sensory neurons.¹ HIV-SN is a typical small-fibre sensory neuropathy. Common symptoms are often accompanied by neuropathic signs such as reduced or absent ankle reflexes, diminished vibration sense and altered sensitivity to light tactile or thermal stimuli.² Distal sensory

polyneuropathy is attributed to axonal degeneration of predominantly small and unmyelinated fibers. Painful dysesthesias, severe burning pain, allodynia, pins and needles sensations and numbness are the main symptoms of HIV-associated distal sensory polyneuropathy. Certain protease inhibitors (PIs) such as indinavir, saquinavir and ritonavir have been implicated in the development of peripheral neuropathy as well. However, incidences tend to be lower compared with those seen with stavudine and didanosine-based regimens.³

The widely used AIDS clinical trials group validated BPNS tool is employed in identifying HIV-SN. It is based on a directed symptom questionnaire and limited clinical examination. HIV-SN is defined as the presence of neuropathic symptoms and at least an abnormal perception of vibrations of a 128 Hz tuning fork on the great toe or abnormal ankle reflexes or both. Numbness had a sensitivity of 86% and a specificity of 81% for the clinical diagnosis of HIV-SN. Asking about numbness had greater sensitivity for the diagnosis of HIV-SN than asking about pain. Reduced or absent ankle Achilles tendon reflex had a sensitivity of 84% and a specificity of 98% for HIV-SN.⁴ HIV-SN presents a number of challenges to the clinician and patient. Diagnostic difficulties arise from a wide differential and the inability to clinically distinguish etiological processes. A delay in diagnosis may lead to a subsequent intractable course.⁵ The cause of neuropathy may be multifactorial. Although HIV itself may cause peripheral neuropathy, co-morbid conditions and medications such as ART and anti-tuberculosis agents also contribute to the high incidence of neuropathy in this population.⁶ Lack of early diagnosis and preventative strategies may result in the necessity to interrupt and substitute ART to alleviate HIV-SN.⁷

The present study was conducted to evaluate the prevalence of peripheral neuropathy in people living with HIV and AIDS on ART so as to help mitigate the burden and enhance care for HIV-seropositive individuals receiving ART.

METHODS

A cross-sectional study was done at the CoE, ART centre, Regional institute of medical sciences (RIMS), Imphal, Manipur over a period of 2 years from September 2017 to August 2019.

Study design

The study design was a cross sectional study.

Study duration

The study duration was from September 2017 to August 2019.

Inclusion criteria

Participants who were more than 18 years of age with diagnosed HIV and AIDS on ART and who gave consent for the study were included in the study.

Exclusion criteria

Participants with history of peripheral neuropathy before starting the ART, diabetes mellitus, cerebrovascular accident, leprosy and tuberculosis on anti-tubercular treatment were excluded from the study.

Sample size

Sample size was calculated by using Fisher's method with a calculated sample size of 198 cases as per the inclusion and exclusion criteria.

Methodology

The study subjects were 198 participants of both sexes who were HIV-seropositive cases on ART. AIDS clinical trials group validated BPNS tool was employed in identifying HIV-SN. This tool is based on a directed symptom questionnaire and limited clinical examination. A detailed history including duration of ART, combination of drugs, time since diagnosis and duration of the symptoms along with the CD4 count was taken into account.

Statistical analysis

The completed questionnaires were checked for completeness, coded and entered in IBM SPSS version 21. Descriptive statistics like percentages, means was used for data summarization and presentation. Inferential statistics like Chi-square test was employed and a $p < 0.05$ was considered as statically significant.

Ethical issues

Ethical approval for the study was obtained from research ethics board, Regional institute of medical sciences, Imphal. Informed consent was taken and confidentiality maintained.

RESULTS

The age distribution showed majority 92 (46.46%) participants in the age between 41-50 years bracket while only 11 (5.56%) were below 30 years of age (Figure 1).

The gender distribution showed male in the majority with 53% (105) while female constituted 47% (93) among the total 198 participants (Figure 2).

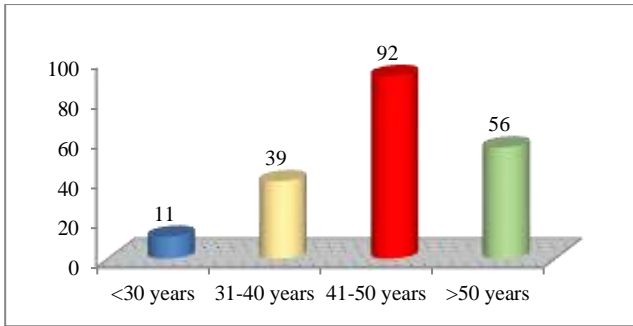


Figure 1: Age distribution among the 198 participants.

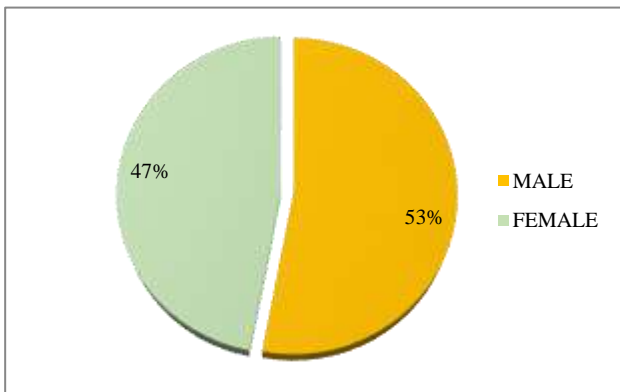


Figure 2: Gender distribution among the 198 participants.

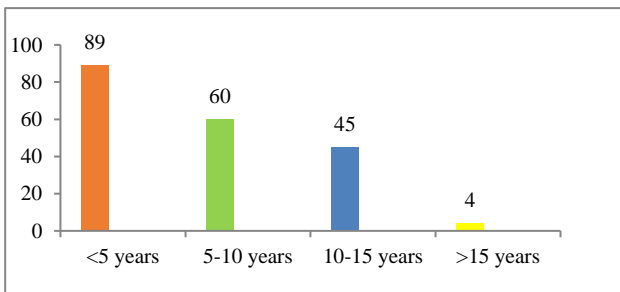


Figure 3: Duration of treatment with ART among the 198 participants.

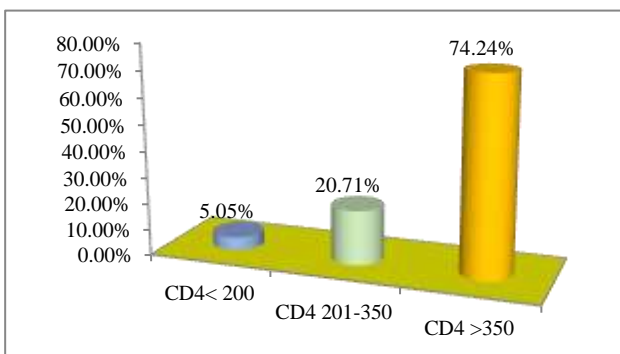


Figure 4: CD4 count distribution among the 198 participants.

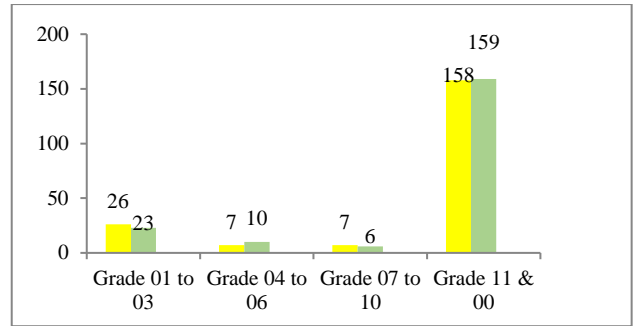


Figure 5: Distribution of neuropathy score in right leg (yellow) and left leg (green) among the 198 participants.

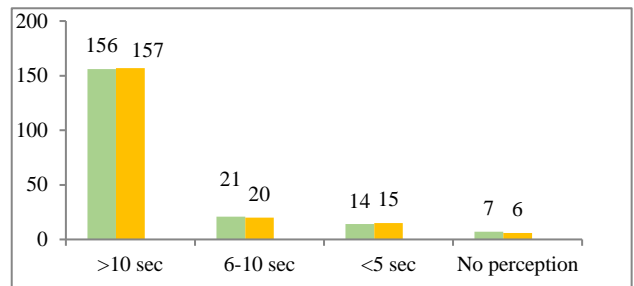


Figure 6: Distribution of vibration sense of right leg (green) and left leg (blue) with relation to time.

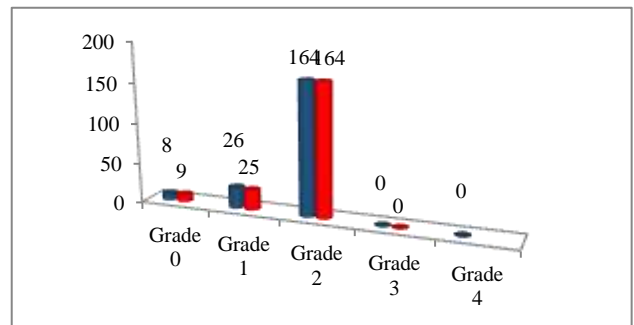


Figure 7: Distribution of participants according to the grade of ankle reflex of right leg (blue) and left leg (red) among the 198 participants.

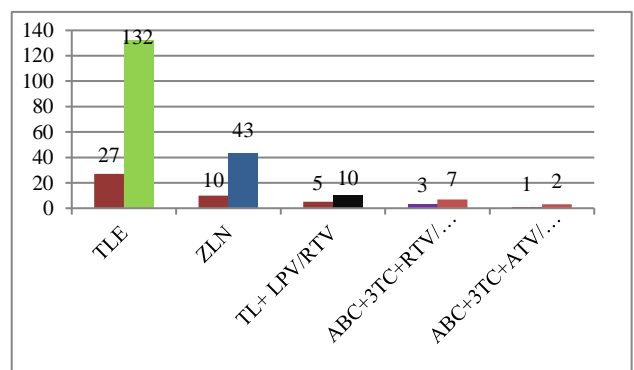


Figure 8: Prevalence of peripheral neuropathy in 46 participants out of 198 with relation to the ART regime.

Table 1: ART regimes distribution among the 198 participants.

ART regimen	Frequency	Percentage
TLE	132	66.7
ZLN	43	21.7
TL+LPV/RTV	10	5.1
ABC+3TC+RTV/LPV	7	3.5
ZL+EFV	3	1.5
ABC+3TC+ATV/LPV	2	1
ABC+3TC+EFV	1	0.5

Table 2: Ankle reflex grading.

Grades	Grading
0	Absent
1	Hypoactive
2	Normal
3	Hyperactive
4	Clonus

ART regimes

Maximums participants were on TLE (tenofovir+lamivudine+efavirenz) regimes which was 132 (66.7%), ZLN (zidovudine+lamivudine+nevirapine) with 43 (21.7%), TL+LPV/RTV (tenofovir+lamivudine+lopinavir/ritonavir) with 10 (5.1%), ABC+3TC+RTV/LPV (abacavir+lamivudine+ritonavir/lopinavir) with 7 (3.5%), ZL+EFV (zidovudine+lamivudine+efavirenz) with 3 (1.5%), ABC+3TC+ATV/LPV (abacavir+lamivudine+atazanavir/lopinavir) with 2 (1%) and ABC+3TC+EFV (abacavir+lamivudine+efavirenz) with 1 (0.5%) respectively (Table 1).

Majority of the participants 89 (44.9%) were on antiretroviral therapy (ART) for less than 5 years while 4 (2%) participants were on ART for more than 15 years (Figure 3). The mean ART duration was 7.02±4.6 years.

CD4 count <200 cumm was seen in 10 (5.05%) participants, 41 (20.71%) participants had CD4 count 201-350 cumm and 147 (74.24%) participants had CD4 count >350 cumm respectively (Figure 4). The mean CD4 count was 562.30±347.59 cumm.

Neuropathy score was classified as grade 1 to 3, grade 4 to 6, grade 7 to 10 and grade 11 and 0. In neuropathy score of right leg, 26 (13.13%) participants fell into the category score range of grade 1 to 3, 7 (3.54%) participants in the category of grade 4 to 6, 7 (3.54%) participants in the score range of grade 7 to 10 and 158 (79.79%) participants fall into the category of grade 11 and 0 (Figure 5). In neuropathy score of left leg, 23 (11.62%) participants fell into the category of grade 1 to 3, 10 (5.05%) participants fell into the category of grade 4 to 6, 6 (3.03%) participants fell into the category of grade 7 to 10 and 159 (80.30%)

participants fall into the category of grade 11 and 0 respectively (Figure 5).

Vibration sense of right leg with relation to time had 156 (78.78%) participants with vibration sense of >10 seconds, 21 (10.61%) participants fall in the category of 6 to 10 seconds, 14 (7.07%) participants fall into the category of less than 5 seconds, 7 (3.54%) participants had no perception of vibration sense (Figure 6). Vibration sense of left leg with relation to time had 157 (79.29%) participants with vibration sense of >10 seconds, 20 (10.10%) participants fall into the category 6 to 10 seconds, 15 (7.58%) participants fall into the category of less than 5 seconds, 6 (3.03%) participants had no perception of vibration sense (Figure 6).

Grade of ankle reflex was categorized according to the response elicited (Table 2). On the right leg ankle reflex had 8 (4.04%) participants in grade 0, 26 (13.13%) participants in grade 1, 164 (82.83%) participants in grade 2 and nil in grade 3 and 4 respectively (Figure 7). While grade of ankle reflex of left leg had 9 (4.54%) participants had grade 0, 25 (12.63%) participants in grade 1, 164 (82.83%) in grade 2 and nil in grade 3 and 4 respectively (Figure 7).

Prevalence of peripheral neuropathy according to ART regimens

46 (23.2%) participants had peripheral neuropathy in view of the presence of neuropathic symptoms and at least an abnormal perception of vibrations of a tuning fork on the great toe or abnormal ankle reflexes or both. While majority of the participants (152) 76.8% had a normal finding. Out of 46 participants with peripheral neuropathy according to BPNS, 27 (58.70%) were on TLE regime, 10 (21.74%) were on ZLN, 5 (10.87%) were on TL+LPV/RTV, 3 (6.52%) were on ABC+3TC+RTV/LPV and 1 (2.17%) participant was on ABC+3TC+ATV/LPV (Figure 8). No peripheral neuropathy was observed in those on ZL+EFV and ABC+3TC+EFV (Figure 8).

DISCUSSION

The presence of peripheral neuropathy was examined by using AIDS clinical trials group validated BPNS tools. The participants were considered as a case of peripheral neuropathy if they have at least one subjective symptoms and objective finding.

46 (23.2%) participants among the total 198 participants had peripheral neuropathy while majority of the participants 76.8% (152) had a normal finding. Among the study population 53.03% (105) participants were male and 46.97% (93) participants were female. Out of 46 participants with peripheral neuropathy, 50% (23) were male and 50% (23) were female. Gender was not independently associated with the development of peripheral neuropathy which is similar to a study done by Skopelitis et al.⁸

CD4 count of less than 200 cumm was seen in 10 (5.05%) participants with no peripheral neuropathy, 12 had peripheral neuropathy among 41 (20.71%) participants with CD4 count 201-350 cumm and 34 had peripheral neuropathy among 147 (74.24%) participants with CD4 count more than 350 cumm. The mean CD4 count was 562.30 ± 347.59 cells per cubic mm similar to a study done by Tumusiime et al who stated that the level of CD4 count was not independently associated with the presence of peripheral neuropathy.⁹

Among those on ART for less than 5 years 16 (17.98%) had peripheral neuropathy out of 89 participants, in the 5 to 10 years group 9 (15%) had peripheral neuropathy out of 60 participants, among the 10 to 15 years group 19 (42.22%) had peripheral neuropathy out of 45 participants and in 4 participants who were on ART for more than 15 years 2 (50%) had peripheral neuropathy. In our study there was a positive association between longer duration of treatment with ART and development of peripheral neuropathy comparable to a study conducted by Robinson-Papp et al.¹⁰

Maximum number of patients were on first line of treatment TLE regimes which was 132 (66.7%), followed by ZLN with 43 (21.7%), TL+LPV/RTV with 10 (5.1%), ABC+3TC+RTV/LPV with 7 (3.5%), ZL+EFV with 3 (1.5%), ABC+3TC+ATV/LPV with 2 (1%) and ABC+3TC+EFV with 1 (0.5%) respectively which was comparable to the finding of Chauhan et al.¹¹

Out of the 46 (23.2%) participants among the total 198 participants who had peripheral neuropathy, 27(20.45%) were from among the 132 participants on TLE, followed by 10(23.25%) from 43 participants on ZLN, 5(50%) from 10 participants on TL+LPV/RTV, 3(42.85%) from 7 participants on ABC+3TC+RTV/LPV and 1(50%) out of 2 participants on ABC+3TC+ATV/LPV. Also patient who were on second line of ART had more percentage of peripheral neuropathy than those patients who were on first line of ART.

In the study 19 patients were on PIs combination out of which 9 (47.36%) had peripheral neuropathy comparing to 37 (20.67%) out of 179 participants who were without PI in their ART regime which was comparable to a study conducted by Peterson et al who stated that protease inhibitor exposure was an unrecognized factor for developing peripheral neuropathy.¹²

Limitations

Due to limited resource gold standard test like nerve conduction test (NCT), computerized quantitative sensory testing (QST) or intra-epidermal nerve fiber density was not done. Also previous history of stavudine and didanosine used were not taken in the study.

CONCLUSION

In our study on 198 HIV-seropositive participants on ART, the development of peripheral neuropathy had positive relation with longer duration of treatment with ART and with those on protease inhibitor combination compared to those without it in the ART regimes. Other factors such as age, gender, weight and CD4 count was not independently associated with the development of peripheral neuropathy in HIV-seropositive individuals on ART.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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