

## PREVALENCE AND CLINICAL PROFILE OF PERIPHERAL NEUROPATHY AMONG HIV PATIENTS VISITING A TERTIARY CARE HOSPITAL IN NORTH KARNATAKA: A CROSS-SECTIONAL OBSERVATIONAL STUDY

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### ABSTRACT

#### Introduction:

Peripheral neuropathy (PN) is one of the most common neurological complications in people living with HIV (PLHIV). The increasing life expectancy of HIV-positive patients due to combination antiretroviral therapy (cART) has led to a growing burden of chronic neurological disorders, particularly HIV-associated peripheral neuropathy (HIV-PN). Despite its high prevalence, HIV-PN remains underdiagnosed, leading to significant morbidity and poor quality of life. The objectives was to assess the prevalence of HIV-PN among HIV-positive individuals and to evaluate the demographic and clinical characteristics associated with HIV-PN.

#### Methods:

A cross-sectional observational study was conducted among 158 HIV-positive patients attending a tertiary care hospital in North Karnataka, India. Diagnosis of peripheral neuropathy was based on clinical symptoms, neurological examination, and nerve conduction studies (NCS). The Total Neuropathy Score (TNS) was used to grade peripheral neuropathy severity.

#### Results:

The prevalence of HIV-PN was 79.7%. The most common symptoms were tingling (85%), burning pain (76%), and numbness (62%), predominantly affecting the lower limbs in a length-dependent manner. Risk factors associated with peripheral neuropathy included longer HIV duration ( $p < 0.001$ ), history of tuberculosis ( $p = 0.002$ ), and exposure to older cART regimens ( $p = 0.001$ ).

#### Conclusion:

The study highlights the high prevalence of HIV-PN and its significant impact on patients. Routine screening, early diagnosis, and management strategies should be incorporated into HIV care programs to improve quality of life.

**Keywords:** HIV, peripheral neuropathy, prevalence, cART, nerve conduction studies

### INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that progressively weakens the immune system by targeting CD4+ T lymphocytes, leading to acquired immunodeficiency syndrome (AIDS). Over the past few decades, the global response to HIV has transformed its prognosis from a fatal disease to

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a chronic, manageable condition, thanks to the widespread availability of antiretroviral therapy (ART). However, despite advancements in treatment, HIV-associated peripheral neuropathy (HIV-PN) remains one of the most prevalent and debilitating neurological complications among people living with HIV (PLHIV).

Peripheral neuropathy (PN) is a frequent yet underdiagnosed complication of HIV infection, affecting between 10% and 50% of patients globally.<sup>(1)</sup> It is characterised by distal sensory loss, burning pain, and motor dysfunction, significantly impairing patients' quality of life.<sup>(2)</sup> The pathogenesis of HIV-PN is multifactorial, involving direct viral neurotoxicity, chronic inflammation, and antiretroviral drug-induced mitochondrial toxicity.<sup>(3)</sup>

Distal sensory peripheral neuropathy (DSPN) is the most common form of HIV-PN, affecting both ART-naïve and ART-experienced individuals. It is characterised by numbness, tingling, burning pain, and sensory loss, primarily in the lower extremities. These symptoms significantly impair mobility, daily activities, and mental well-being, often leading to decreased quality of life and increased healthcare burdens. The burden of HIV-PN is particularly significant in resource-limited settings like India, where over 2.3 million people are living with HIV. Despite the availability of combination antiretroviral therapy (cART), neuropathy remains underdiagnosed and undertreated, mainly due to the absence of standardised diagnostic tools, a lack of clinician awareness, and limited access to specialised neurological assessments.

Although several studies have investigated HIV-PN prevalence and pathogenesis, many questions remain unanswered. This study aims to explore the prevalence of HIV-PN in India, where data on neuropathy among PLHIV is scarce, the impact of ART on neuropathy risk, particularly with newer ART regimens, and the effectiveness of a simple, low-cost diagnostic tool to facilitate early detection and intervention. Given that many HIV-infected individuals, especially in India, do not have access to specialized neurological care, a reliable, easy-to-use diagnostic method for non-physician healthcare workers is essential to improve early detection and management.

Significant research has shown that HIV-PN arises from multiple mechanisms, including direct viral neurotoxicity, chronic immune activation, and ART-induced mitochondrial dysfunction. Historically, older ART drugs, particularly nucleoside reverse transcriptase inhibitors (NRTIs) like stavudine (d4T), didanosine (ddl), and zalcitabine (ddC), were found to be neurotoxic, increasing the risk of neuropathy. While the phasing out of these drugs has reduced the incidence, HIV-PN continues to persist in ART-experienced patients due to cumulative neurotoxicity. Additionally, inconsistent diagnostic criteria and varied study methodologies have led to widely differing prevalence estimates, ranging from 11% to 56% globally.

In resource-limited settings such as India, the burden of HIV is substantial, with 23.48 lakh PLHIV as per the National AIDS Control Programme (NACP) released in 2019.<sup>(4)</sup> The prevalence of peripheral neuropathy in PLHIV varies widely due to differences in ART regimens, genetic factors, nutritional status, and co-infections such as tuberculosis and hepatitis C.<sup>(5)</sup>

Despite these insights, several gaps remain in our understanding of HIV-PN. There is no standardised test for diagnosing HIV-PN, and current methods, such as nerve conduction studies (NCS), lack sensitivity for detecting small fibre neuropathy, which often precedes the more apparent symptoms of DSPN. Moreover, studies investigating the prevalence of HIV-PN in India are limited, making it difficult to assess its true burden. Furthermore, there is uncertainty regarding the neurotoxic potential of newer ART regimens and their impact on the long-term risk of neuropathy in HIV patients.

Despite its high prevalence, routine screening for peripheral neuropathy in HIV clinics is not widely practised, leading to delayed diagnosis and suboptimal management. Given the chronic nature of HIV-PN, understanding its epidemiology is crucial for early intervention and targeted therapy.

This study addresses these gaps by investigating the prevalence, risk factors, and clinical characteristics of HIV-PN among PLHIV in India. Additionally, it aims to evaluate a simple, cost-effective diagnostic tool that can be used in resource-limited settings to facilitate early identification and treatment. Given the growing burden of HIV-related neurological

complications, early detection and intervention are critical in improving patient outcomes, reducing disability, and enhancing the quality of life of those affected.

By bridging the knowledge gap in HIV-PN research and introducing a practical diagnostic approach, this study aspires to make a significant contribution to the public health response to HIV in India.

### Objectives

1. To determine the prevalence of HIV-associated peripheral neuropathy in a tertiary care setting and to characterise the spectrum of neuropathic symptoms among HIV-positive patients
2. To identify the demographic and clinical risk factors associated with peripheral neuropathy

### METHODOLOGY

This was a cross-sectional observational study conducted at the outpatient/inpatient department in a government hospital attached to the Karnataka Medical College and Research Institute (KMCR), Hubballi, a city in the southern Indian state of Karnataka from January 2023 to December 2023. A total of 158 consecutive HIV-positive adult patients attending the ART Centre and Medicine OPD were enrolled in the study, regardless of the presence or absence of symptoms suggestive of peripheral neuropathy (PN).

Patients on previously neurotoxic antiretrovirals such as stavudine were excluded, as this agent has been phased out in India following the National AIDS Control Organisation (NACO) guidelines. Concomitant drug use was documented, especially drugs known to cause neuropathy, such as isoniazid and metronidazole. Patients on anti-tubercular therapy received pyridoxine supplementation as per standard protocol. Adherence was assessed via self-reporting and pharmacy refill data, categorised as good (>95%), fair (80–95%), or poor (<80%). The study excluded those patients with pre-existing diabetes mellitus or other known causes of neuropathy (e.g., chronic alcohol use, vitamin B12 deficiency), and those with a history of neuromuscular disorders unrelated to HIV.

Detailed demographic and clinical data (age, sex, body mass index, duration of HIV infection) were collected, including ART regimen, duration of therapy, concomitant medications, adherence history, and any prior opportunistic infections (OIs). Peripheral neuropathic symptoms were assessed using a questionnaire and thorough neurological assessment was done for sensory testing – vibration sensation (128 Hz at great toe and ankle joint), temperature sensation (hot and cold testing), pain sensation (pinprick), and deep tendon reflexes (ankle, knee, wrist, and elbow joints).

Electrophysiological testing was performed in the form of nerve conduction studies (NCS) which measures the electrical conduction of peripheral nerves in upper limb (median and ulnar nerves) and lower limb (Common peroneal, tibial, and sural nerves) by measuring the parameters – Motor nerve conduction velocity (NCV), Sensory NCV, Compound motor action potential (CMAP), sensory nerve action potential (SNAP), distal latency, and F-wave latency. This helps differentiate axonal degeneration from demyelination, providing an objective confirmation of the peripheral neuropathy and classifying its severity. The gathered data was used to calculate the Total Neuropathy Score (TNS), to quantify peripheral neuropathy severity on a scale of 0 to 44.

The Total Neuropathy Score (TNS) is a composite clinical and electrophysiological scoring system used to assess the severity of peripheral neuropathy (PN) in patients. It combines symptom evaluation, clinical examination, and nerve conduction study (NCS) findings to provide a standardised measure of peripheral neuropathy severity.

Components of TNS:

1. Symptom Score (presence and severity of pain, numbness, tingling)
2. Pinprick Sensation (assessed using standard sensory testing)
3. Vibration Perception (tested with a tuning fork at 128 Hz)
4. Strength Testing (manual muscle testing of distal limb muscles)
5. Deep Tendon Reflexes (patellar and Achilles reflexes)
6. Nerve Conduction Studies (NCS) Findings (motor and sensory nerve parameters)

Scoring System:-

Mild Neuropathy: TNS score <10  
 Moderate Neuropathy: TNS score 10–20  
 Severe Neuropathy: TNS score >20  
 Maximum Score: 44

The TNS provides a quantitative and objective assessment of neuropathy, enabling standardised comparisons and aiding clinical decision-making.

The data was coded and recorded in an MS Excel spreadsheet program, and Windows SPSS v23 was used for data analysis. The prevalence was calculated as the proportion of HIV patients diagnosed with peripheral neuropathy. Associations between clinical parameters and peripheral neuropathy were analysed using chi-square tests and logistic regression. The Mantel-Haenszel method was used to measure the strength of the association between HIV-PN and covariates, and a final model was made using logistic regression. Crude and adjusted Odds Ratios (OR), together with their 95% Confidence Intervals (95% CI), were reported. A p-value <0.05 was considered statistically significant.

The study was approved by the Institutional Ethics Committee, and informed consent was obtained from all participants.

## RESULTS

Among the 158 patients, 101 (63.9%) were male and 57 (36.1%) female, with a mean age of 39.2 ± 7.4 years. Of the total study participants (n=158), 79.7% (n=126) had symptomatic peripheral neuropathy and 20.3% (n=32) were asymptomatic.

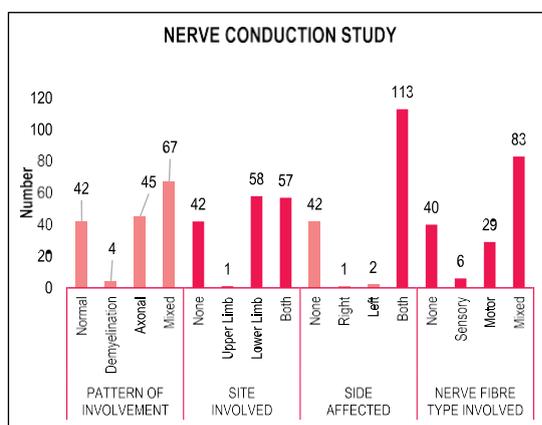


Figure 1. Summary of the NCS results in all study participants (n=158)

Among the symptomatic participants, 99.2% (n=125) had bilateral, symmetrical involvement, while one participant had unilateral (right side) symptoms. (Figure 1)

Among those with peripheral neuropathy, both feet were involved in 98.3%, both legs in 97.5%, both hands and fingers in 80.8%, and both the forearms and arms in 1.6% of the participants. This finding is consistent with the “stocking and glove” pattern of peripheral neuropathy involvement in 98.4% (n=124), while 1.6% (n=2) had localised neuropathy. (Figure 1)

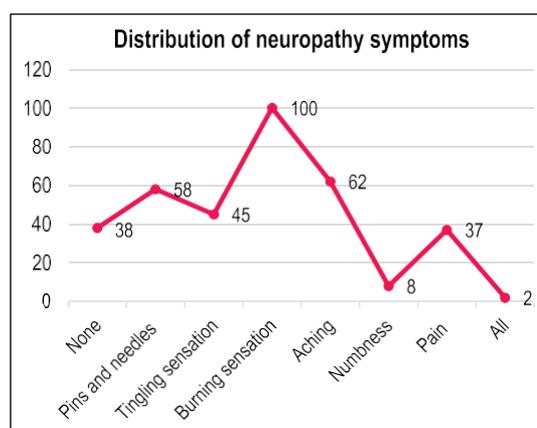


Figure 2. Distribution of peripheral neuropathy (PN) symptoms among the study participants.

Among the study participants (n=158), burning sensation was present in 63.3% (n=100) tingling sensation in 28.5% (n=45), pins and needles sensation was noted in 36.7% (n=58), aching sensation in 39.2% (n=62), numbness in 5.1% (n=8), and pain sensation in 23.4% (n=37). The rest 24% (n=32) were asymptomatic. (Figure 2)

Figure 3 summarizes the neurological examination findings among all 158 study participants. The most commonly observed abnormalities included impaired vibration sense (56 participants), impaired pinprick sensation (56), absent or areflexia (68), and mild distal muscle weakness (83). Ankle reflexes were absent or diminished in a significant proportion (87), and gait abnormalities (mild to moderate) were noted in 65 participants. These findings reflect a predominantly sensory and areflexic pattern consistent with HIV-associated distal symmetrical polyneuropathy.

Out of 158 HIV-positive patients, 126 (79.7%) were diagnosed with peripheral neuropathy. Of these:

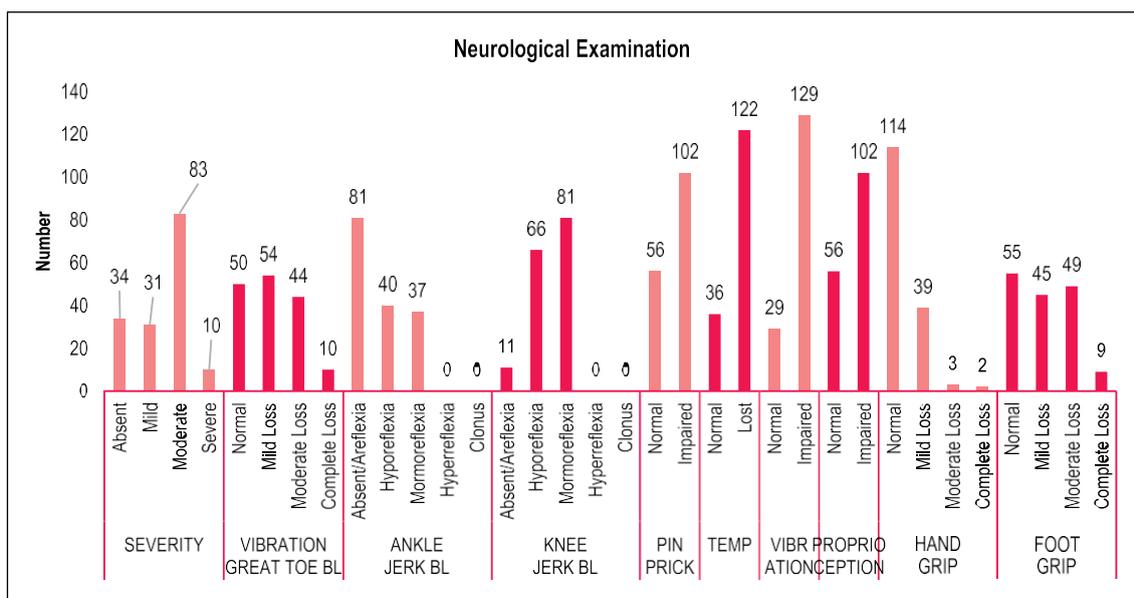


Figure 3. Summary of neurological examination in all study participants (n=158)

- Mild peripheral neuropathy: 32 patients (25.3%)
- Moderate peripheral neuropathy: 67 patients (53.2%)
- Severe peripheral neuropathy: 27 patients (21.4%)

All patients were on combination antiretroviral therapy (cART), with the most common regimens being TDF/3TC/EFV (n=101, 63.9%), AZT/3TC/NVP (n=45, 28.4%), and PI-based regimens (n=12, 7.6%). None of the patients were on stavudine-containing regimens.

Concomitant medications included cotrimoxazole (n=133, 84.1%), isoniazid (n=19, 12%)—all of whom received pyridoxine 10 mg/day—and metronidazole (n=9, 5.7%). No patients were on chemotherapy or other known neurotoxic drugs.

Adherence to ART was good in 138 (87.3%) patients, fair in 15 (9.5%), and poor in 5 (3.2%). Common co-existing opportunistic infections included tuberculosis (n=18, 11.4%), oral candidiasis (n=10, 6.3%), and one case each of cryptococcal meningitis and herpes zoster.

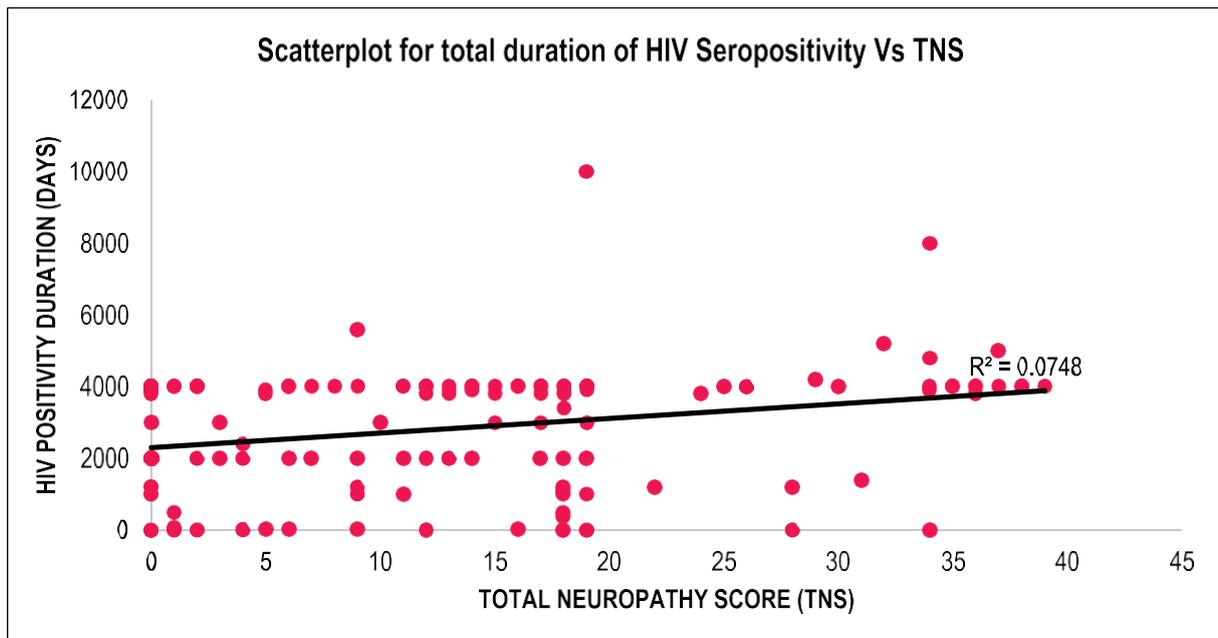
Electrophysiological Findings (NCS Subgroup Analysis, n=115) (Figure 1)

- Axonal degeneration: 67 patients (58.3%)
- Demyelination: 28 patients (24.3%)
- Mixed pattern: 20 patients (17.4%)

The factors associated with severe peripheral neuropathy included those with longer HIV duration: OR 2.1 (95% CI: 1.4–3.2, p<0.001), patients with previous exposure to stavudine: OR 3.5 (95% CI: 2.0–6.1, p=0.001) and patients with a lower CD4 count (<350 cells/mm<sup>3</sup>): OR 1.9 (95% CI: 1.1–3.4, p=0.02)

The present study revealed that patients with a longer duration of HIV (mean: 7.3 years) had a significantly higher prevalence of peripheral neuropathy (p<0.001). It was also evident that those individuals with past exposure to stavudine (d4T) and zidovudine (AZT), were strongly associated with peripheral neuropathy (p=0.001).

There was no strong correlation between current CD4 count and peripheral neuropathy severity (p=0.48) in the present study. However, patients with a lower baseline CD4 count (<350 cells/mm<sup>3</sup>) had a significantly higher risk of peripheral neuropathy. Also, the body mass index (BMI) and other metabolic factors (e.g., diabetes, dyslipidemia) did not show a strong correlation in this study.



**Figure 4.** Scatterplot diagram for total duration of HIV Seropositivity vs TNS in the present study ( $r^2 = 0.07482$ )

The scatter plot depicts the relationship between the total neuropathy score (TNS) and the duration of HIV seropositivity (in days). The analysis revealed no significant correlation between the duration of HIV infection and the severity of peripheral neuropathy, as indicated by the low Pearson correlation coefficient ( $r = 0.07482$ ). This suggests that the length of time since HIV diagnosis may not independently predict neuropathy severity in this cohort. (**Figure 4**)

**Figure 5** illustrates the mean Total Neuropathy Score (TNS) across various clinical and treatment-related subgroups. Participants with peripheral neuropathy symptoms had a significantly higher mean TNS score (16.49) compared to those without symptoms (3.5). Among WHO AIDS stages, the highest mean TNS was observed in Stage 3/Staged disease (19.06/44), followed by Stage 2 (15.41/44), indicating a progressive rise in neuropathy severity with advancing immunosuppression. Patients on zidovudine-based regimens (TLE/ZLN/LE/ALE) exhibited a higher mean TNS (17.5/44) than those on TLD (13.96/44), suggesting a possible association between specific ART drugs and neuropathy severity.

## DISCUSSION

This study aimed to characterise the burden of peripheral neuropathy (PN) and identify risk factors among HIV-positive patients.

The prevalence of HIV-associated PN in our cohort was 79.7%, which is consistent with reports from other low- and middle-income countries. For instance, a study from Nigeria by Adeleke et al. <sup>(15)</sup> (2022) reported a PN prevalence of 27.1%, with higher rates observed among patients on zidovudine-based regimens. Similarly, Mellors et al. <sup>(16)</sup> (2021) in South Africa noted a 32% prevalence among patients on first-line ART, linking higher risk with older age and low CD4 counts.

Mehta et al. <sup>(17)</sup> (2023) from North India reported a lower prevalence (15%), possibly due to earlier initiation of ART and absence of zidovudine use. Another study by Dube et al. <sup>(18)</sup> (2020) in Malawi found that patients with poor adherence and longer duration of HIV infection had a significantly higher risk of developing PN.

Our findings support these observations, with neuropathy more commonly seen in patients on zidovudine and those with poor adherence or co-existing TB. None of our patients were on stavudine, which has been strongly implicated in mitochondrial toxicity and is no longer recommended under NACO guidelines.

We acknowledge that isoniazid, though supplemented with pyridoxine, may still contribute to PN, especially in malnourished individuals. Cotrimoxazole and metronidazole, used by a subset of patients, are also known to occasionally contribute to neurotoxicity.

The robust association between advanced age (>40 years) and peripheral neuropathy (AOR 1.82) fulfils the objective of identifying risk factors, reinforcing age as a critical predictor. Conversely, the lack of significant links between peripheral neuropathy and gender ( $p=0.43$ ) or education ( $p=0.328$ ) aligns with the study's exploration of sociodemographic variables, though conflicting literature (e.g., Sindie et al. (9) on gender) underscores the complexity of these relationships.

This study introduces two novel contributions to the literature on HIV-associated peripheral neuropathy:

1. **Age as a Modifiable Risk Factor:** While aging is widely recognised in peripheral neuropathy pathophysiology, this study reframes advanced age (>40 years) as a modifiable risk factor in the context of modern antiretroviral therapy (ART). With HIV populations aging globally due to ART success, proactive management of age-related comorbidities like peripheral neuropathy becomes actionable rather than inevitable.
2. **Context-Specific Sociodemographic Nuances:** The lack of association between peripheral neuropathy and gender/education in this cohort contrasts sharply with studies from regions with pronounced socioeconomic disparities (e.g., Vecchio et al. (11), Sindie et al. (9)). This highlights that peripheral neuropathy risk mediators—such as occupational hazards, nutrition, or healthcare access—may operate differently across settings, challenging the universality of sociodemographic risk models.

These findings carry significant implications for clinical and public health practice:

1. **Aging HIV Populations:** As individuals with HIV live longer, the high prevalence of peripheral neuropathy (79.7%) signals an urgent need to integrate neuropathy screening into routine HIV care to prevent disability and preserve quality of life.
2. **Resource Allocation:** The strong age- peripheral neuropathy association suggests prioritising older patients in screening programs, optimising limited resources in high-burden regions.
3. **Revisiting “One-Size-Fits-All” Assumptions:** The divergent sociodemographic findings underscore that peripheral neuropathy risk factors are context-

dependent. Policies must adapt to local realities rather than relying on generalised global guidelines.

The high peripheral neuropathy prevalence compared to global estimates may reflect regional differences in ART regimens (e.g., stavudine use), genetic susceptibility, or diagnostic practices. While the age-peripheral neuropathy association is consistent worldwide, conflicting sociodemographic findings highlight gaps in understanding how cultural, occupational, or economic contexts modulate risk. For instance, gender disparities in manual labour or nutrition access in certain regions might indirectly heighten peripheral neuropathy risk, masking associations in more equitable settings. Hence, it is advisable to revise the national HIV guidelines in high-prevalence regions to mandate peripheral neuropathy monitoring, aligning with WHO's focus on HIV-related comorbidities

In resource-limited settings, nutritional deficiencies, particularly vitamin B12 and folate deficiency, may exacerbate nerve damage, compounding the effects of HIV and ART-induced neurotoxicity. Additionally, the higher prevalence of tuberculosis (TB) and anti-tubercular therapy (ATT) exposure in this cohort could contribute to neuropathy, as drugs like isoniazid are known neurotoxins. Chronic immune activation and systemic inflammation due to untreated opportunistic infections or late HIV diagnosis may also accelerate neuronal degeneration. Furthermore, socioeconomic factors such as poor healthcare access, delayed ART initiation, and reliance on older neurotoxic ART regimens (e.g., stavudine) may explain the higher neuropathy burden compared to global estimates. These contextual nuances suggest that peripheral neuropathy in HIV patients is not solely a consequence of ART but a multifactorial condition influenced by broader health and economic disparities.

## CONCLUSION

This study confirms a high prevalence (79.7%) of peripheral neuropathy in HIV-positive individuals, with tingling, burning pain, and numbness being the most common symptoms. Longer HIV duration, lower baseline CD4 count, and exposure to neurotoxic ART regimens (stavudine, zidovudine) were significant risk factors. Given the chronic and debilitating nature of HIV-PN, routine screening, early ART modifications, and better pain management strategies should be prioritised in HIV care programs.

While this study establishes a strong association between HIV-associated peripheral neuropathy (HIV-PN) and aging, future research should explore the longitudinal progression of peripheral neuropathy in HIV-positive individuals, particularly in the era of newer antiretroviral therapy (ART) regimens. Prospective studies could clarify whether early ART modifications or adjunct neuroprotective therapies slow peripheral neuropathy progression. Additionally, further investigations into genetic predisposition, metabolic risk factors (e.g., diabetes, vitamin deficiencies), and inflammatory biomarkers could refine predictive models for peripheral neuropathy. Cost-effectiveness analyses of routine peripheral neuropathy screening programs in resource-limited settings would also be valuable to inform scalable public health interventions.

### Strengths and Limitations

Strengths include a gender-balanced cohort (68.4% male vs. 31.6% female), enhancing representativeness for similar HIV care settings, and rigorous adjustment for age-related confounders. However, the cross-sectional design precludes causal inference, and unmeasured variables (e.g., ART drug toxicity, diabetes, or vitamin deficiencies) may bias peripheral neuropathy risk estimates. Additionally, the homogeneous education levels in our sample might obscure socioeconomic gradients observed in other studies (e.g., Vecchio et al. <sup>11</sup>).

### Key Recommendations:

1. Regular screening for peripheral neuropathy in all HIV-positive patients, especially those with longer disease duration.
2. Early switch from stavudine/zidovudine to safer ART options (tenofovir-based regimens).
3. Use of nerve conduction studies (NCS) for diagnosis in high-risk patients.
4. Further research on neuroprotective strategies to prevent or delay peripheral neuropathy progression.

### CONFLICT OF INTEREST

None

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