International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

A Study on the Correlation between CD4COUNT and Peripheral Neuropathy in HIV Positive Patients

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OPEN ACCESS

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Received: 04-01-2026
Accepted: 23-01-2026
Available online: 01-02-2026

ABSTRACT

Background: Peripheral neuropathy is a common and debilitating neurological complication in people living with Human Immunodeficiency Virus (HIV). It significantly affects quality of life and functional capacity. The degree of immunosuppression, reflected by CD4 T-lymphocyte count, is believed to play an important role in the development and severity of HIV-associated peripheral neuropathy.
Objectives: To study the association between CD4 count and the presence of peripheral neuropathy in HIV-positive patients.
Methods: This cross-sectional observational study was conducted among HIV-positive patients attending a tertiary care centre. Clinical evaluation for symptoms and signs of peripheral neuropathy was performed using standardized neurological examination. CD4 counts were obtained using flow cytometry. Patients were categorized based on CD4 count levels, and the prevalence of peripheral neuropathy across these groups was analysed. Statistical analysis was carried out to assess the association between CD4 count and peripheral neuropathy.
Results: Peripheral neuropathy was found to be more prevalent among male patients with lower CD4 counts.
Conclusion: Peripheral neuropathy is significantly associated with low CD4 counts in HIV-positive patients. Early identification of neurological symptoms and regular monitoring of CD4 levels may aid in timely intervention, thereby reducing morbidity and improving quality of life in this population.

Keywords: *Peripheral neuropathy, CD4 counts, HIV-positive patients, Human Immunodeficiency Virus (HIV), Anti-Retroviral Therapy (ART), Highly Active Anti-Retroviral Therapy (HAART).*

INTRODUCTION

HIV infection continues to pose a major global public health challenge, with nearly 39 million people affected worldwide, predominantly in low- and middle-income countries [1]. Although combination antiretroviral therapy has significantly reduced mortality and transformed HIV into a chronic manageable disease, long-term complications—particularly neurological manifestations—remain important contributors to morbidity [2]. Among neurological complications, peripheral neuropathy is the most common, causing significant disability through chronic pain, sensory disturbances, and gait impairment, and occurs more frequently in patients with advanced disease and immunosuppression [3,4].

HIV-associated peripheral neuropathy is most commonly seen as distal symmetric polyneuropathy, characterized by stocking–glove sensory symptoms with minimal motor involvement [5]. Its pathogenesis is multifactorial, involving direct viral neurotoxicity, immune-mediated mechanisms, chronic inflammation, mitochondrial dysfunction, opportunistic infections, nutritional deficiencies, and neurotoxic effects of certain antiretroviral drugs such as stavudine and didanosine [6].

CD4 T-lymphocyte count remains a key indicator of immune status and disease progression in HIV infection. Declining CD4 counts are strongly associated with increased risk of neurological complications, including peripheral neuropathy [7]. Multiple studies have demonstrated a higher prevalence and greater severity of peripheral neuropathy in patients with lower CD4 counts, supporting a direct link between immunosuppression and peripheral nerve damage through mechanisms such as increased viral replication and neurotoxic cytokine release [8,9].

Epidemiology

The prevalence of peripheral neuropathy in HIV-positive individuals varies widely, ranging from 20% to over 60%, influenced by factors such as ART exposure, duration of infection, diagnostic criteria, and degree of immunosuppression [3,5]. Although ART has reduced severe immunosuppression, peripheral neuropathy remains common even in patients with virological suppression [10]. Studies have consistently shown a higher risk of neuropathy with declining CD4 counts; Schifitto et al. reported increased distal sensory polyneuropathy in patients with CD4 counts <200 cells/mm³ [4], while Ellis et al. demonstrated a strong association with nadir CD4 counts in the ART era [10]. In developing countries, including India, the burden is further increased due to delayed diagnosis, late ART initiation, and coexisting conditions such as malnutrition and tuberculosis [11,12]. Indian studies have similarly reported high neuropathy prevalence, particularly in patients with low CD4 counts and advanced disease [13]. Given its high prevalence yet frequent underdiagnosis, understanding the relationship between CD4 count and peripheral neuropathy is essential for early intervention and improved outcomes, forming the basis of the present study.

AIM

To study the association between CD4 count and the presence of peripheral neuropathy in HIV-positive-AIDS patients.

METHODOLOGY

Study Design and Setting

This was a hospital-based cross-sectional observational study conducted in the Department of Medicine at ICTC center, Guntur Government General Hospital, (GGH) GUNTUR. The study was carried out over a defined study period after obtaining approval from the Institutional Ethics Committee.

Duration of the study: January 2023 to June 2024 (18 months)

Source of the data: Patients who are diagnosed HIV positive and currently on treatment in ICTC center GGH, GUNTUR, during period of 18 months

Study Population

The study included HIV-positive patients diagnosed with HIV/AIDS, aged 18 years and above, currently on treatment in ICTC center GGH, GUNTUR, during period of 18 months

Inclusion Criteria

- Age ≥18 years who are HIV positive and on treatment in ICTC Guntur.
- Patients willing to participate and provide informed written consent
- Patients with a known neurological disorder.
- Patients on older regimens didanosine (ddI, Videx), zalcitabine (ddC, Hivid), and stavudine (d4T, Zerit)

Exclusion Criteria

- Patients with known causes of peripheral neuropathy other than HIV (e.g., diabetes mellitus, chronic alcoholism, renal failure, hypothyroidism, vitamin B12 deficiency)
- History of exposure to neurotoxic drugs unrelated to antiretroviral therapy like metronidazole, chemotherapy
- Patients with acute critical illness or pre-existing neurological disorders
- Patients who are not willing for study.
- Patients diagnosed with TB and on treatment.

Sample Size and Sampling Method

A total of 150 patients were enrolled in the study using a consecutive sampling method, based on inclusion and exclusion criteria.

Data Collection

After obtaining informed consent, demographic and clinical data including age, gender, duration of HIV infection, and CD4 count were recorded using a structured proforma. A detailed clinical evaluation was then performed to assess symptoms suggestive of peripheral neuropathy, such as numbness, tingling, burning sensation, and pain. Peripheral neuropathy was clinically suspected based on features of distal symmetric polyneuropathy, and where feasible, standardized neuropathy screening tools were used to support the clinical diagnosis.

All participants subsequently underwent a comprehensive neurological examination to evaluate sensory, motor, and

reflex abnormalities. The degree and severity of peripheral neuropathy were objectively assessed using surface nerve conduction studies (NCS), which measured parameters including nerve conduction velocity, latency, and amplitude in selected peripheral nerves.

Following neurological assessment, peripheral venous blood samples were collected under aseptic precautions for the estimation of CD4 T-lymphocyte counts. CD4 counts were measured using standard flow cytometry techniques and were recorded and analyzed in relation to the presence and severity of peripheral neuropathy. Based on CD4 count, patients were categorized into 2 groups (e.g., <185 cell/mm3 and >185cells/mm³) to analyse the relationship with peripheral neuropathy.

Statistical Analysis

Data were entered into Microsoft Excel and analysed using statistical software such as SPSS. Descriptive statistics were used to summarize demographic and clinical variables. The association between CD4 count and peripheral neuropathy was analysed using Chi-square test. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with ethical standards and the Declaration of Helsinki. Confidentiality of patient information was maintained, and participation was entirely voluntary, with the option to withdraw from the study at any time. Institutional ethics committee approval was obtained for conducting the study.

RESULTS

A total of 150 HIV patients were enrolled in the study. Amongst them 58.7% of patients exhibiting peripheral neuropathy, while 41.3% showed no evidence of neuropathy, indicating that more than half of the HIV-positive patients were affected. Figure 1 depicts the prevalence of peripheral neuropathy in the study population.

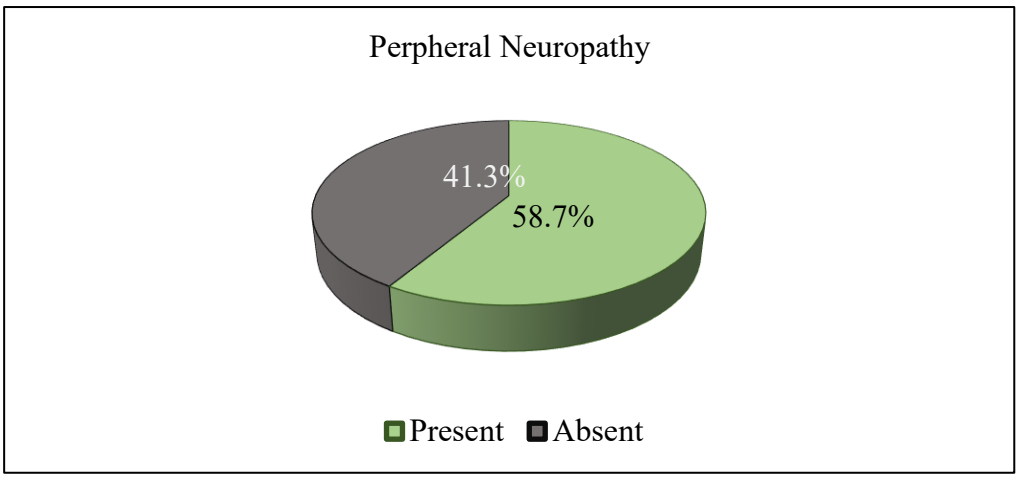

Figure: 1 Prevalence of peripheral neuropathy in the study population.

Table:1 Distribution based on Age group

	Peripheral neuropathy		
Age group in years	Yes	No	Total (%)
< 40 years	52 (55.9%)	41 (44.1%)	93 (100%)
> 40 years	36 (63.2%)	21 (36.8%)	57 (100%)
Total	88 (58.7%)	62 (41.3%)	150 (100%)
Chi-square test = 0.76, p = 0.38 (Not statistically significant)			

Among patients aged <40 years, 55.9% had peripheral neuropathy while 63.2% patients aged >40 years had peripheral neuropathy. Although a higher proportion of peripheral neuropathy was observed in patients older than 40 years, the difference was not statistically significant (p = 0.38).

Table:2 Distribution based on Gender

	Peripheral neuropathy		
Gender	Yes	No	Total (%)
Female	47 (48%)	51 (52%)	98(100%)
Male	41 (78.8%)	11 (21.2%)	52(100%)
Total	88 (58.7%)	62 (41.3%)	150(100%)
Chi-square test = 13.39, p < 0.001 (Statistically significant)			

In the present study Peripheral neuropathy was more common in males (78.8%) than in females (48%). The association between male gender and peripheral neuropathy was statistically significant ($\chi^2 = 13.39$, $p < 0.001$), indicating that male HIV-positive patients were significantly more likely to develop peripheral neuropathy in the present study.

Table:3 Association between CD4 Count and Peripheral Neuropathy

	Peripheral neuropathy		
CD4 count (cells/mm³)	Yes	No	Total (%)
< 185	63 (75%)	21 (25%)	84(100%)
> 185	25 (37.9%)	41 (62.1%)	66 (100%)
Total	88 (58.7%)	62 (41.3%)	150 (100%)
Chi-square test = 20.86, p = 0.0001 (Statistically significant)			

Peripheral neuropathy was markedly more common (75%) among patients with CD4 counts below 185 cells/mm³, where three-fourths of patients were affected. The association between CD4 count and peripheral neuropathy was highly statistically significant.

Table 4: Association between d4T Regimen and Peripheral Neuropathy

	Peripheral neuropathy		
ART regimen	Yes	No	Total (%)
Non-d4T containing	24 (40%)	36 (60%)	60(100%)
d4T containing	64 (71.1%)	26 (28.9%)	90(100%)
Total	88 (58.7%)	62 (41.3%)	150(100%)
Chi-square test = 14.27, p = 0.0001 (Statistically significant)			

Peripheral neuropathy was substantially more common among patients receiving d4T-containing antiretroviral regimens (71.1%) compared to those on non-d4T regimens (40%). The association was statistically significant, indicating that d4T use is strongly associated with an increased risk of peripheral neuropathy.

Table 5: Association between Duration of HIV Infection and Peripheral Neuropathy

	Peripheral neuropathy		
Duration in Years	Yes	No	Total (%)
0 — 1 years	1 (7.7%)	12 (92.3%)	13 (100%)
1 — 3 years	6 (18.8%)	26 (81.2%)	32 (100%)
4 — 6 years	29 (58.0%)	21 (42.0%)	50 (100%)
>7 years	52 (94.5%)	3 (5.5%)	55 (100%)
Total	88 (58.7%)	62 (41.3%)	150 (100%)
Chi square test= 64.16 p=0.0001*, statistically significant			

Peripheral neuropathy increased significantly with longer duration of HIV infection, with the highest prevalence seen in patients infected for more than seven years, indicating that prolonged disease duration is a strong risk factor, likely due to cumulative viral neurotoxicity, chronic immune activation, and prolonged antiretroviral exposure.

DISCUSSION

In the present study, peripheral neuropathy was identified in 58.7% of the 150 HIV-infected patients. This prevalence is slightly higher than that reported by Damien et al. [14] where 58% of patients experienced neuropathic pain based on the Tibt test, and considerably higher than the Gunashekaran et al where the prevalence was 43.3% [15]. The relatively high prevalence observed in this study may be explained by multiple factors. The inclusion of 150 patients provided a sufficiently robust sample, and the utilization of nerve conduction studies likely enhanced the detection of peripheral neuropathy. Given their high sensitivity, nerve conduction studies may identify subclinical or early neuropathic changes, thereby contributing to higher prevalence estimates compared with studies relying on clinical criteria alone.

Additionally, demographic and clinical characteristics of the study population influence neuropathy prevalence. The Damien et al.study emphasized the role of viral load and HAART regimen, noting a higher risk among patients with elevated viral loads and those receiving neurotoxic agents such as stavudine.[14] Similarly, the Gunashekaran et al study reported that increasing age and advanced HIV disease stage were significantly associated with higher neuropathy prevalence (43.3%), findings that are relevant to the current study, where many patients may have been in advanced stages of infection.[15]

In contrast, Amiji et al. [16] reported a lower prevalence of peripheral neuropathy (14.1%) among HIV infected children in Tanzania, underscoring the influence of age on neuropathy development. This supports the observation that adult HIV patients are at greater risk, likely due to prolonged exposure to HIV infection and antiretroviral therapy.

Overall, the higher prevalence of peripheral neuropathy in the present study highlights the importance of comprehensive diagnostic strategies, including nerve conduction studies, and underscores the need for targeted interventions in high-risk HIV populations. Variability in prevalence across studies reflects differences in diagnostic methods, demographic profiles, and clinical characteristics, emphasizing the complexity of peripheral neuropathy management in HIV.

Peripheral neuropathy was more common in patients aged >40 years (63.2%) compared to those <40 years (55.9%), but the association with age was not statistically significant in the present study. Similarly, Damien et al. [14] reported no significant association between age and peripheral neuropathy, with an overall prevalence of 58%, highlighting the influence of viral load and HAART regimen. In contrast, Gunashekaran et al. [15] observed a higher prevalence of peripheral neuropathy (43.3%) in patients aged >40 years, while Amiji et al. [16] reported a much lower prevalence (14.1%) among children and adolescents. Werimo et al. [17] also demonstrated a marginal increase in risk with advancing age (odds ratio 1.04). These findings indicate that although peripheral neuropathy tends to be more frequent in older patients, its occurrence is influenced by multiple demographic and clinical factors rather than age alone.

Peripheral neuropathy was present in 48 % of females and 78.8% of males. The association between gender and peripheral neuropathy was statistically significant ($\chi^2 = 13.39$, $p < 0.001$), indicating that male HIV-positive patients were significantly more likely to develop peripheral neuropathy than females in the present study. Similar findings were reported in Gunashekaran et al. [15] and Werimo et al. [17] (males 55%, females 45%).

Peripheral neuropathy was more prevalent among patients with CD4 counts <185 cells/mm³ (71.6%) compared to those with CD4 counts ≥185 cells/mm³ (28.4%). The association between CD4 count and peripheral neuropathy was highly statistically significant, indicating that lower CD4 counts are strongly associated with an increased risk of peripheral neuropathy. This finding underscores the role of advanced immunosuppression in the development of HIV-associated peripheral neuropathy.

Studies from the USA also demonstrated an association between advanced disease and peripheral neuropathy, with CD4 counts <200 conferring odds ratios of 1.39 and 1.64, respectively [18,19].

In contrast, Gunashekaran et al. [15] reported that 34.6% of patients with peripheral neuropathy had CD4 counts <200, with no increased risk observed at lower CD4 levels, suggesting that neuropathy in patients with CD4 counts >200 may be related to drug toxicity or other underlying conditions [20]. Similarly, Werimo et al. [17] found that CD4 count at HIV diagnosis and current CD4 count had no effect on the presence of peripheral neuropathy, and viral load suppression was also not associated with neuropathy. Studies from Kenya [21], Uganda [22], Rwanda [23], and Zimbabwe [24] likewise demonstrated no significant association between CD4 counts and peripheral neuropathy. In Amiji et al. [16] the odds of developing peripheral neuropathy was significantly high among children with severe immunosuppression as reflected by a low CD4 count < 350 cell/mm^3 and a high viral load ≥ 1000 copies/ml.Overall, while lower CD4 counts were associated with a higher prevalence of peripheral neuropathy in the present study, evidence from other populations suggests that additional factors such as antiretroviral drug exposure and nutritional status play an important role in the development of peripheral neuropathy.

In the present study,patients with HIV duration ≥7 years showed the highest prevalence of neuropathy (71.6%), compared to 4–6 years (23.9%) and 0–3 years (4.5%).Peripheral neuropathy increased with longer duration of HIV infection and was significantly more common in patients with disease duration exceeding seven years, indicating that prolonged infection is a strong risk factor, likely due to cumulative viral effects, chronic immune activation, and extended antiretroviral exposure. In Werimo et al. [17], a longer duration of follow-up had a slight positive association with the occurrence of peripheral neuropathy.

Significant positive association between the duration of clinical follow up and peripheral neuropathy was demonstrated in a study done in North America in 2006 [25]. More recent studies in Rwanda [23] and Nigeria [26] also show the same association.

In Damien et al study [14], Duration of diagnosis with HIV did not significantly determine the occurrence of neuropathic pain. Similar findings were reported in Gunashekaran et al. [15].

Amiji et al. [16] there was no significant association observed between peripheral neuropathy and the duration of HIV infection. Similar findings were also reported in previous studies involving children [27,28]. This could be possibly be explained by the fact that most of HIV infection in children results from vertical transmission from mother to child, thus

unlike adults' time of diagnosis does not reflect the time of infection in this population.

Peripheral neuropathy was significantly more frequent among patients receiving d4T-containing ART regimens (71.1%) compared to those on non-d4T regimens (40%), confirming a strong association between stavudine use and neuropathy. Similar findings were reported by **Gunasekaran et al [15]**, who observed a slightly higher prevalence of peripheral neuropathy among stavudine users, suggesting drug toxicity as an important contributory factor. Notably, during the initial period of HAART (<12 months), neuropathy occurred equally in patients on stavudine and non-stavudine regimens, indicating a role of the disease process itself early on. However, with increasing duration of HAART, a higher number of neuropathy cases were observed among stavudine users, supporting the view that late-onset peripheral neuropathy is more likely related to stavudine-induced neurotoxicity.

In the present study peripheral neuropathy increased with longer duration of HIV infection, rising from **1.1%** in the first year to **59.1%** after seven years. While **Werimo et al. [17]** similarly identified long HIV duration as a risk factor, **Damien et al. [14]** and **Gunashekaran et al. [15]** reported no significant association, indicating variability in the influence of disease duration across studies.

CONCLUSION

Peripheral neuropathy was a frequent complication among HIV patients. Male gender, CD4 count, use of stavudine-containing regimens, and longer duration of HIV infection and antiretroviral therapy were significantly associated with neuropathy. These findings highlight the need for early diagnosis, regular neurological screening, careful antiretroviral selection, and close immune monitoring to reduce neuropathy risk in HIV patients.

DECLARATION

Conflicts of interests: The authors declare no conflicts of interest.
Author contribution: All authors have contributed in the manuscript.
Author funding: Nill

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