Peripheral Neuropathy in HIV-infected children attending Care and Treatment Clinic, at Muhimbili National Hospital, Dar es Salaam: A Cross sectional study

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Abstract

Background: Peripheral neuropathy (PN) is a neurological complication of untreated Human Immunodeficiency Virus (HIV) infection or exposure to antiretroviral drugs.

Objectives: To determine the prevalence and associated factors for peripheral neuropathy among children living with HIV, attending Care and Treatment Clinic (CTC) at Muhimbili National Hospital (MNH).

Materials and Methods: A cross-sectional study was conducted at MNH-CTC in Dar es Salaam between October - December 2019, where 383 HIV positive children aged 5 to 18 years were enrolled. Baseline characteristics were obtained from participant's medical records at enrollment. Screening for peripheral neuropathy was done on each participant using the Pediatric modified Total Neuropathy Score (Ped m TNS) screening tool. Continuous variables were summarized as mean ($\pm$ standard deviation) or median (Interquartile range) and differences compared using student t-test or Mann-Whitney U test. Categorical variables were summarized as frequencies and differences compared using chi square or Fisher's exact test. Logistic regression models were applied to determine the independent predictors of peripheral neuropathy on multivariate analysis, reported as odds ratios (ORs) and 95% confidence intervals (CI).

Results

The prevalence of peripheral neuropathy among HIV infected children was 14.1% (95% CI (10.8% - 18%). Common neuropathic presentation was numbness and tingling sensation, reduced ankle reflexes, loss of vibration sense and reduced light touch and sensation to pain limited to fingers and toes. Severe immunosuppression reflected by CD4 count < 200 cell/mm³ (OR=5.21; 95% CI 2.0 – 13.57; $p = 0.001$), high viremia ≥ 1000 copies/ml (OR=26.31; 95% CI 7.91 – 86.51; $p < 0.001$), use of a combination regimen containing NRTI plus PI (OR= 5.67; 95% CI 2.11– 15.22; $p = 0.01$) and time interval of at least ≥ 6 months since last use of isoniazid (OR=3.35; 95% CI 1.41 – 7.91; $p = 0.006$) were independent predictors for peripheral neuropathy.

Conclusion

Peripheral neuropathy is common among HIV infected children attending CTC at MNH and its frequency increases with advanced disease. The choice of antiretroviral regimen and other medications with potentially neurotoxic effect should be carefully done. Early screening for peripheral neuropathy among HIV positive children should be done routinely in CTCs.

Background

Peripheral neuropathy (PN) is a frequent neurological complication of Human Immunodeficiency Virus (HIV). The incidence increases with advanced disease or severe immunosuppression. It can be a result of cytopathic effects of the virus or the neurotoxic effects of certain antiretroviral medications that causes inflammatory mediated neuronal cell damage. (1) Though these mechanisms differ in etiopathogenesis, the disorder is clinically and physiologically indistinguishable. In low income countries HIV infected children are at a higher risk to develop neurological complications because they also face multiple comorbidities such as anemia, tuberculosis, syphilis, herpes, malnutrition and poor socio-economic status which further compound the pathology and complicate it's management.(2) Clinically, there is no standard definition of diagnosing peripheral neuropathies. Patients may be asymptomatic or can experience one or more of the following symptoms : pain, numbness, tingling, aching, burning sensation in a glove and stocking distribution, reduced ankle reflexes and decreased pinprick and vibration sensation in the distal lower extremities.(1), (3), (4) The gold standard for diagnosis of PN is electrophysiological tests or skin biopsy which is invasive, costly and requires a high level of expertise for its interpretation, hence it cannot be done routinely. Several clinical screening tools that are user friendly and cost effective have been developed to screen for HIV associated PN. (3)· (5) Currently, there is no approved treatment for PN, but several drugs have been suggested for symptomatic control of neuropathic pain such as anticonvulsants like gabapentin and pregabalin, topical capsaicin patches, antidepressants, and nonspecific analgesics such as nonsteroidal anti-inflammatory drugs and opioids. This study aims to evaluate the magnitude of PN among HIV infected children using a simple clinical screening tool. This will facilitate early detection of this condition so that timely interventions can be offered to prevent its progression to debilitating symptoms later in life.

Materials And Methods

A hospital based cross sectional study was conducted at HIV Care and Treatment Clinic (CTC) at Muhimbili National Hospital (MNH) in Dar es Salaam during the months of October to December 2019. Our study population comprised of all confirmed HIV positive children attending CTC from 5– 18 years of age who were verbally competent. Children who had neurological impairment like cerebral palsy, stroke or spinal cord pathologies that would interfere with neurological examination were excluded from the study. Children who met the inclusion criteria were consecutively recruited into the study until the desired sample size was reached. The laboratory diagnosis of HIV infection at MNH in infants and children < 18 months is done by detection of viral nucleic acid (RNA or pro-viral DNA) or viral antigens (p24) and in > 18 months by detecting antibodies to HIV using rapid tests or Enzyme Immunoassays (EIA) according to Tanzanian National AIDS Control Program guidelines. (6). Data was recorded in a structured questionnaire designed for this study, which was pilot tested to ensure validity of the questions. (*Supplementary File 1*)

Information regarding demographic characteristics, anthropometric measurements (body mass index (BMI) and height for age using the WHO classification system) to determine nutritional status, HIV disease and drug information was obtained from the patient's clinic card and medical records available during their current clinic visit. Each patient was screened using the Pediatric modified Total Neuropathy Score (Ped m TNS) screening tool that consists of subjective and objective assessment of sensory, motor, and autonomic domains of the peripheral nervous system.

This tool has been used to screen children with chronic illness such as cancer and diabetes mellitus for peripheral neuropathies. (7), (8) The tool was translated into Swahili version which is the local language spoken in Tanzania and pre-tested in a pilot study to know if participants understood the questions and the description of symptoms. Objective assessment was done to determine light touch and pain sensation that was elicited in different dermatomes in the distal extremities using 10 grams Semmes Weinstein monofilament and Medipin (with patient's eyes closed) respectively, if the subject responded to the stimuli then it was normal for that extremity. Otherwise, further testing was done in more proximal areas of the limb. Vibration sensation was elicited by 128 Hz tuning fork placed perpendicular to the bony prominences (fingers, wrist, elbows, toes, and ankles) the cut off was at least 10 seconds followed by testing for deep tendon reflexes. A score of 4 and above on the Ped m TNS was used to define the presence of neuropathy. (*Supplementary File 2*)

The variables measured in this study were age, sex, BMI and height for age, hemoglobin levels, CD4 cell count, HIV viral load, WHO clinical stage, duration of HIV illness, type, and duration of Anti-retroviral Therapy (ART) use, isoniazid exposure and cotrimoxazole prophylaxis.. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range) respectively and t - test was used to determine the differences between means and their significance. Mann-Whitney *U*test was used to compare continuous variable with non-parametric distribution. Categorical variables were expressed as frequencies and group differences were compared using chi -square and Fisher's exact test. Logistic regression models were applied to determine the independent predictors of peripheral neuropathy. Results are reported as odds ratios (ORs) and 95% confidence intervals (CI), p values < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of four hundred and forty-five (445) HIV infected children attended CTC follow up clinic during the study period. Three hundred and eighty-three (383) participants met the set inclusion criteria, and gave consent, thus were randomly enrolled in the study. (Fig. 1)

Out of the study participants, males were 61% (237/383), the median age, height and weight was 14 years (IQR 9–17), 148 cm (IQR 129–156) and 38 kg (IQR 25–46) respectively. Majority of the participants (228/383; 59.5% and 232/383; 60.6 % respectively) had their BMI and height for age within normal range. The median duration of HIV illness among participants was 12 years (IQR 8–16) and 67.6% (259/383) were classified into WHO clinical disease stage III and IV. Almost all children were using ART during enrollment, with the combination of Nucleoside Reverse Transcriptase Inhibitor (NRTI) plus Dolutegravir (DTG) (243/383; 63.4%) being frequently used among participants. Most of the participants reported to have used isoniazid as part of Isoniazid Preventive Therapy (IPT) or anti-TB treatment during HIV-TB coinfection (359/383; 93.7%) and cotrimoxazole prophylaxis (348/383; 90.9%) as indicated in the Tanzania national guidelines for management of HIV. (Table 1)

Table 1 : General characteristic of children screened for HIV associated PN

Characteristics	N = 383 (%)	
<i>Patient related factors</i>		
Age (years)		
5-9		95 (24.8 %)
10-14		117 (30.5 %)
15- 18		171 (44.6 %)
Sex		
Male		237 (61.9 %)
Female		146 (38.1 %)
Nutritional Status BMI (kg/m²)		
Normal		228 (59.5 %)
Underweight		155 (40.5%)
Height/Age		
Normal		232 (60.6%)
Stunting		151 (39.4%)
<i>Disease related factors</i>		
CD4 counts (cells/mm³)		
< 200		37 (9.7%)
≥ 200		346 (90.3%)
Viral Load (copies/ml)		
< 1000		262 (68.4%)
≥ 1000		121 (31.6%)
WHO clinical stage		
1 and 2		124 (32.4%)
3 and 4		259 (67.6%)
Median duration of HIV illness (years)		12 years (IQR 8 - 16)
<i>Drug related factors</i>		
Median duration of all ARV's used (years)		12 years (IQR 8 - 16)
Median duration of ARV subgroups (years)		
NRTI + NNRTI's	8	8
NRTI + PI's	14	
NRTI + DTG		
Types of ARV used by all patients in the study		
NRTI's + NNRTI's		65 (17 %)
NRTI's + PI's		75 (19.6%)
NRTI's + DTG		243 (63.4%)
Isoniazid Exposure		
Yes		359 (93.7 %)
No		24 (6.3%)
Cotrimoxazole Prophylaxis		
Yes		348 (90.9%)
No		35 (9.1%)

HIV associated PN

The prevalence of PN in this study was 14.1 % (54/383) based on the assessment done using the Ped m-TNS(Fig. 1). Symptomatic patients frequently presented with numbness (85.21%), and tingling sensation (61.11 %). Frequent examination findings were reduced ankle reflexes (88.81 %) and reduced pain sensation (72.22 %) (Table 2)

Table 2: Prevalence of symptoms and signs in children with PN (n= 54)

SYMPTOMS	N (%)
Numbness	46/54 (85.21%)
Burning Sensation	7/54 (13.0 %)
Tingling Sensation	33/54 (61.11 %)
SIGNS	
Ankle reflex	
Reduced	32/54 (59.24 %)
Light touch	
Reduced	48/54 (88.81 %)
Pain Sensation	
Reduced	39/54 (72.22 %)
Vibration sense	
Reduced	21/54 (38.87 %)

Amongst those screened for HIV associated PN 14.4% (21/146) were females and 16.4% (28/171) belonged to age group of 5–18 years. Nearly a quarter (24%) of children with PN used ART combination of NRTI's plus PI that include *Abacavir/ Lamivudine with Lopinavir/ritonavir* and *Zidovudine / Lamivudine with Lopinavir/ritonavir*. PN was observed more in HIV infected children with CD4 count < 200 cells/mm³ (59.5% vs 40.5%, *p* = 0.0001). The median duration of HIV illness and ART use was longer (13 years: IQR 8–15) in children who had PN compared to those who did not have PN (12 years: IQR 8–15). We also observed that 15% (54/359) participants who had isoniazid exposure were found to have PN. (Table 3)

Table 3: distribution of demographic and clinical characteristic of 383 hiv infected children screened for peripheral neuropathy.

Variable	PN Present N (%)	PN Absent N (%)	*p- value
Patient related factors			
Age (years)			
5-9	8 (8.3%)	88 (91.7%)	0.9
10-14	18 (15. 5%)	88 (84.5%)	
15-18	28 (16. 4%)	143 (83.6%)	
Sex			
Male	33 (13.9%)	204 (86.1%)	0.02
Female	21 (14.4%)	125 (85.6%)	
Mean Hemoglobin (g/dl)	10.3 ± SD 1.4	10.5 ± SD 1.5	0.96 ^b
BMI (kg/m²)			
Normal	36 (15.8%)	192 (84.2%)	0.25
Underweight	18 (11.6%)	137(88.4%)	
Height/Age			
Normal	29 (12.5%)	203 (87.5%)	0.26
Stunting	25 (16.6%)	126 (83.4%)	
-			
Disease related factors			
CD4 count (cells/mm³)			
< 200	22 (59.5%)	15 (40.5%)	0.0001
≥ 200	32 (9.2 %)	314 (90.8%)	
Viral load (copies/ml)			
< 1000	7 (2.7 %)	255 (97.3%)	0.0001
≥ 1000	47 (38.8%)	74 (61.2%)	
WHO Clinical Stage			
Stage 1 & 2	7 (5.6%)	117 (94.4%)	0.001
Stage 3 & 4	47 (18.1%)	212 (81.9%)	
Median duration of HIV illness (years)	13 (IQR 8 - 15)	12 (IQR 8-16)	0.66 ^a
Drug related factor			
Median duration of ARV use (years)			
	13 (IQR 8 -15)	12 (IQR 8-16)	0.65 ^a
ARV drug combination groups			
NRTI's + NNRTI's	7 (10.8 %)	58 (89.2%)	0.02
NRTI's + PI's	18 (24 %)	57 (76 %)	
NNRTI's + DTG	29 (11.9 %)	214 (88.1%)	
Isoniazid Exposure			
Yes	54 (15 %)	305 (85 %)	0.02 ^c
No	0	24 (100 %)	
Time interval since last use of Isoniazid			
< 6 months	11 (8.9 %)	137 (92.6%)	0.003
≥ 6 months	43 (18.3 %)	216 (81.7 %)	
Cotrimoxazole Prophylaxis			
Yes	48 (14.4%)	298 (85.6%)	0.43 ^c
No	4 (11.4%)	1. (88.6%)	

*P- value < 0.05 is significant

^a - Mann Whitney U test; ^b - Independent samples t-test; ^c - Fishers Exact Test

In a multivariate analysis model adjusted for age, sex, CD 4 cell counts, viral load, ART combinations, WHO clinical stage and isoniazid exposure. We found that low CD4 count < 200 cell/mm³ (OR = 5.21; 95% CI 2.0–13.57; p = 0.001), a high viral load (OR = 26.31 ; 95% CI 7.91–86.51; p = 0.0001), the use of ART combination containing NRTI's plus PI's (OR = 5.67; 95% CI 2.11–15.22; p = 0.01) and the time interval of least ≥ 6 months since last use of isoniazid (OR = 4.54; 95% CI 1.91–10.79; p = 0.001) were independent predictors of PN. (Table 4)

Table 4: Univariate and multivariate analysis of factors associated with HIV - PN

Characteristic	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Patient related factors				
Age (years)				
5-9	1		1	
10-14	2.43 (0.97- 6.07)	0.06	2.52 (0.74 - 8.56)	0.11
15-18	2.46 (1.03 - 5.87)	0.04	3.68 (1.08 - 12.49)	0.18
Sex				
Male	0.96 (0.53 - 1.73)	0.9	-	-
Female	1			
Mean Hemoglobin (g/dl)	1.01 (0.84 - 1.19)	0.96	-	-
BMI (kg/m²)				
Normal	1			
Underweight	0.7 (0.38 - 1.28)	0.25	-	-
Height/Age				
Normal	1			
Stunting	1.38 (0.77 - 2.47)	0.26	-	-
Disease related factors				
CD4 counts (cells/mm³)				
< 200	14.4 (6.78 - 30.41)	0.0001	5.21 (2.0 - 13.57)	0.001
≥ 200	1		1	
Viral Load (copies/ml)				
< 1000	1		1	
≥ 1000	23.13 (10.01 -53.34)	0.0001	26.31 (7.91 - 86.51)	0.0001
WHO clinical stage				
1 & 2	1		1	
3 & 4	3.7 (1.62 -8.46)	0.002	0.43 (0.12 - 1.58)	0.21
Duration of HIV illness (years)	1.0 (0.95 - 1.07)	0.73	-	-
Drug related factors				
ARV drug combinations				
NRTI + NNRTI	0.89 (0.37 - 2.13)	0.79	1.13 (0.32 - 4.01)	0.84
NRTI + PI	2.33 (1.21 - 4.49)	0.01	5.67 (2.11- 15.22)	0.01
NNRTI + DTG	1		1	
Duration of ARV use (years)	1.01 (0.95 - 1.07)	0.72	-	-
Isoniazid Exposure				
Yes	0.01 (0 - ∞)	0.99	-	-
No	1			
Time interval since last use of Isoniazid				
< 6 months	1		1	
≥ 6 months	2.78 (1.38 - 5.61)	0.004	4.54 (1.91-10.79)	0.001
Cotrimoxazole Prophylaxis				
Yes	0.76 (0.26 - 2.27)	0.63	-	-
No	1			

Discussion

This study aimed to determine the prevalence of PN and associated factors among children living with HIV who attended CTC follow up clinic at Muhimbili National Hospital. The result from this study shows that the prevalence of PN in HIV positive children attending CTC at MNH is 14.1%. The prevalence of HIV

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associated PN in children varies greatly among studies from different countries ranging from 13–34 %. (16),(17),(18), (25) The prevalence from this study was consistent with a study done in HIV infected Peruvian children who were diagnosed using electrophysiological tests. (11) However, higher rates have been found in South African and Brazilian children who were diagnosed using clinical scoring tools like Neuropathy Symptom Score (NSS)/Neuropathy Disability Score (NDS) and electrophysiological studies respectively.(15), (16), (17) The variability in results could be attributed to the diversity of patient population and the various methods used to diagnose neuropathies in different studies, where some clinicians used clinical scoring tools while others used electrophysiological studies. Despite the variation in the population demographics, the prevalence of PN obtained in HIV positive children using clinical scoring tool was almost similar to that obtained from electrophysiological studies. (11), (43)

Predictors of PN among HIV infected children.

In this study the independent predictors of PN among HIV infected children attending CTC at MNH were severe immunosuppression as reflected by a low CD 4 counts $< 200\text{cell/mm}^3$, a high viral load ≥ 1000 copies/ml, use of ARV regime containing a combination of NRTI's plus PI's and the time interval of at least ≥ 6 months since last use of isoniazid. These factors have also been observed to be strong predictors of PN in both children and adults living with HIV in different settings. (10),(13),(14),(15)

Clinical presentation

Using the Ped m TNS screening tool predominant neuropathic symptoms reported by participants in our study were numbness and tingling sensation in the distal lower limbs. They also had reduced ankle reflexes, sensation to light touch and pain that was limited to the toes and few had reduced vibration sense. These findings were comparable to a study done by Remco et al, who assessed HIV associated PN in children using a different clinical neuropathy screening tool.(12) In HIV positive adults it has been observed that in addition to the neuropathic symptoms patients also had significant functional impairment like fatigue, slower gait, poor cognitive functioning and depression compared to those who did not have PN.(13)

It has been highlighted in previous reports that many patients have subclinical neuropathy during evaluation that was either co-incidentally detected by electrophysiology studies or during a skin biopsy. (15) This could also explain the difference in reporting the clinical presentation across studies since many patients could be asymptomatic at presentation, and would not meet the diagnostic criteria of a clinical scoring tool and could be missed during a clinical evaluation. However, despite the limitations of the clinical scoring tools, in this study the tool identified children with PN who had never been diagnosed before., This shows its usefulness in a routine care settings where healthcare workers often depend on caregivers to subjectively report history of such symptoms. Thus, findings from this study emphasize a role of regular active assessment of PN for all HIV positive children attending CTC follow up clinic using a standard tool.

Patient related factors

In this study PN was equally distributed among males and females and was more common in older children above the age of 10 years. Similarly, Floeter et al, reported that the risk of PN in HIV infected children was higher in older children above 13 years old than younger ones.(14) Few adult studies have also shown association of PN with older and taller patients regardless of whether they had received ART. (16) When the two factors were combined neuropathy rates increased from 18% in younger and shorter patients to 33% in younger, taller patients, the cut off age being ≤ 40 years and height ≥ 170 cm.(17) This combination has not been observed in children. One plausible explanation for the discrepancy in these results may be because older ones can easily express their symptoms than young ones.

We observed no significant difference in relation to sex, age and hemoglobin levels among those with or without PN. Furthermore, contrary to a study involving HIV positive children (11) which showed that children with malnutrition had a higher risk to develop distal sensory PN than those who did not have malnutrition, we observed no association between malnutrition and HIV associated PN. This could be explained by the fact that in our study very few children had malnutrition and those who had malnutrition did not have the severe forms.

Disease related factors

The odds of developing PN were significantly high among children with severe immunosuppression as reflected by a low CD4 count $< 200\text{ cell/mm}^3$ and a high viral load ≥ 1000 copies/ml in this study. Similar observation has been reported in earlier studies involving adults before ART became widely available. (19),(20) In contrast, few reports involving children and adults during ART era have not shown association between immunosuppression and advanced disease with PN despite several studies suggesting that low CD4 cell counts represents a risk factor for HIV neuropathy. (12),(21),(22) This could be due to early initiation of ART and other unstudied risk factors that may have attributed to PN observed in these population.

Moreover, the fact that majority of children enrolled in the current study were using ART's, and some were observed to have neuropathy, suggests a possibility of a subclinical PN that was not detected before initiation of ART as baseline screening is not routinely done in children attending CTC follow up clinics.(15)

Patients with long standing HIV infection could theoretically be at greater risk for peripheral nerve damage. In this study no significant association was observed between PN and the duration of HIV infection since diagnosis. Similar findings were also reported in previous studies involving children. (9), (12) This could be possibly be explained by the act 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. However, longer duration of HIV related systemic symptoms have been found in adult population who were diagnosed with PN compared to those who did not have PN. (19) Possible risk factors for instance alcohol use, opportunistic infections, HIV related malignancies, prolonged exposure to neurotoxic medications and environmental exposures may at least partially account for the high neuropathy rates observed in adults with longer duration of HIV infection than in children. (2),(15)

Drug related factors

There was a significant association between the use ART that contained NRTI's plus PI's with PN in this study. Previous studies have shown that some of the NRTI's can cause PN in both adults and children, particularly the dideoxy-NRTI's (d – drugs) like stavudine, didanosine, and zalcitabine which are known to cause mitochondrial damage in the peripheral nerves. (24),(25),(26) These drugs have been phased out from the ART regimens for both children and adults living with HIV, and none of the participants in our study were using antiretroviral regimen combination containing d-drugs. Few studies involving adults also showed that the use of PI's like indinavir, lopinavir and saquinavir in the ART regime was associated with peripheral neuropathies.(18),(27) However, the role of PI induced neuropathy is still unclear and the independent risk of neuropathy attributable to PI's is likely to be small and outweighed by its vital role in viral suppression in the ART regimens. (21) Furthermore, drug induced toxic neuropathy despite being clinically and electrophysiologically indistinguishable from HIV associated PN it is dose dependent and reversible, thus patients on ART needs a close evaluation.

There was a significant association between the time interval of at least ≥ 6 months since last use of isoniazid prior to the study and occurrence of PN. Isoniazid is commonly used medication in Tanzania, either for HIV-TB co-infection and as part of IPT in HIV infected children and adults. Majority of the participants attending CTC follow up clinic reported that they were prescribed isoniazid either currently or in the past at a dose of 10mg/kg. Isoniazid induced neuropathy is dose dependent and it has been extensively reported in literature.(22)-(23) There is no clear demarcation on the dose and duration of onset of symptoms after initiating isoniazid. Isoniazid reduces the biological active pyridoxine (Vitamin B6) that regenerates and nourishes nerve cells. Thus it is recommended that patients using isoniazid must also receive Vitamin B6 supplements, to prevent development of isoniazid-induced peripheral neuritis (24). Unfortunately, none of the participants in our study who were using isoniazid as part of IPT or TB treatment were receiving pyridoxine. Thus, the observed association between the use of isoniazid and occurrence of neuropathy in this study could be because the pyridoxine supplementation was not implemented as recommended.

This study had some limitations. Firstly, this was a cross sectional study limited by ability to establish a causal relationship. Secondly, HIV associated PN was based on a clinical diagnosis therefore its incidence may have been underestimated since electrophysiologic studies or skin biopsies were not performed. Lastly, none of the participants had a baseline neuropathy screening done before initiating or changing ART which made it difficult to establish the attributing factor causing injury to the peripheral nerves whether it was HIV related or drug induced neurotoxicity. Despite the limitations the study provides a study has identified a neglected problem among HIV infected children, showing the importance of routine assessment for PN in HIV clinics.

Conclusion

HIV associated PN is common in Tanzanian children attending CTC at MNH. Advanced disease, use of ART regimen containing NRTI's and PI's and the time interval of at least ≥ 6 months since last use of isoniazid were independent predictors for HIV associated PN in this study.

All HIV positive children should have a baseline neuropathy screening for PN prior to initiating and a follow up routine screening that enable us to differentiate drug induced neurotoxicity from HIV related PN. The combination regimen in the ART regimen and other drugs for treating comorbid conditions should carefully be selected and pyridoxine supplementation should be given to children using isoniazid to prevent the development of PN. Further research should aim to explore the individual side effect of the antiretroviral drugs that could potentially be neurotoxic in children especially the role of PI's as early identification could prevent progression to severe debilitating or irreversible PN.

List Of Abbreviations

3TC Lamivudine

ABC Abacavir

AIDS Acquired Immunodeficiency Syndrome

ART Antiretroviral Therapy

AZT Zidovudine

BMI Basal Metabolic Rate

BPNS Brief Peripheral Neuropathy Score

CD 4 Cluster of Differentiation

CHARTER CNS HIV Anti-Retroviral Treatment Effects Research

CTC Care and Treatment Clinic

DRG Dorsal Root Ganglia

DTG Dolutegravir

DNA De-oxy ribonucleotide acid

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EID Early Infant Diagnosis

GABA_A Gamma Amino Butyric Acid type A

HAART Highly Active Anti-Retroviral Therapy

HIV Human Immunodeficiency Virus

IFN Interferon Gamma

IL Interleukin

IPT Isoniazid Preventive Therapy

ISN Isoniazid

LPV/R Lopinavir/ritonavir

MNH Muhimbili National Hospital

NDS Neuropathy Disability Score

NNRTI Non- Nucleoside Reverse Transcriptase Inhibitors

NRTI Nucleoside Reverse Transcriptase Inhibitors

NSS Neuropathy Symptom Score

Ped- m TNS Pediatric- Modified Total Neuropathy Score

PEPFAR President's Emergency Plan for AIDS Relief

PI Protease Inhibitor

PMTCT Prevention of Mother to Child Transmission

RCH Reproductive and Child Health

TDF Tenofovir

TNF Tumor Necrosis Factor

UNAIDS Joint United Nations Program on HIV and AIDS

UNICEF United Nations Children's Emergency Fund

WHO World Health Organization

Declarations

Ethics Declaration

This study was approved by the Muhimbili University of Health and Allied Sciences (MUHAS) ethical review board with approval number DA.287/298/01A. **All methods** were carried out **in accordance** with relevant guidelines and regulations. Permission to conduct this study at the Care and Treatment Clinic at MNH was granted by hospitals' respective research office.

Written informed consent was sought from the caregiver of the child and a formal written assent was also obtained from all children seven years and above who had the capacity to understand at a level they could comprehend using Swahili language.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are not publicly available because participants have not given consent for public availability of their data. However, the data are available from the corresponding author on reasonable request.

Competing interests

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None

Author's Contributions

IA conceptualized the study design, reviewed study tools and did the data collection. EK and LM assisted with the logistics in the screening of peripheral neuropathy at the HIV CTC follow up clinic at MNH. IA and HN participated in data analysis and writing the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Patient recruitment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFile1QuestionnaireEnglishPeripheralNeuropathyinHIVinfectedchildrenattendingCareandTreatmentClinicatMuhimbiliNationalHospitalDares](#)
- [SupplementaryFile2ThePediaticmodifiedTotalNeuropathyScoretool.docx](#)