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RESEARCH REPORT

Clinical diagnosis of sensory neuropathy in HIV patients treated with tenofovir: A 6-month follow-up study

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Abstract

Background: Sensory neuropathy (SN) is a common and often painful neurological condition associated with HIV-infection and its treatment. However, data on the incidence of SN in neuropathy-free individuals initiating combination antiretroviral therapies (cART) that do not contain the neurotoxic agent stavudine are lacking.

Aims: We investigated the 6-month incidence of SN in ART naïve individuals initiating tenofovir (TDF)-based cART, and the clinical factors associated with the development of SN.

Methods: 120 neuropathy-free and ART naïve individuals initiating cART at a single center in Johannesburg, South Africa were enrolled. Participants were screened for SN using clinical signs and symptoms at study enrolment and approximately every 2-months for a period of ~6-months. Diagnostic criteria for symptomatic SN was defined by the presence of at least one symptom (pain/burning, numbness, paraesthesias) and at least two clinical signs (reduced vibration sense, absent ankle reflexes or pin-prick hypoaesthesia). Diagnostic criteria for asymptomatic SN required at least two clinical signs only (as above).

Results: A total of 88% of the cohort completed three visits within the 6-month period. The 6-month cumulative incidence of neuropathy was 140 cases per 1000 patients (95% CI: 80-210) at an incidence rate of 0.37 (95% CI: 0.2-0.5) per person year. Height and active tuberculosis (TB) disease were independently associated with the risk of developing SN ($P < .05$).

Interpretation: We found that within the first 6 months of starting cART, incident SN persists in the post-stavudine era, with 11 (9%) of individuals developing asymptomatic SN, and 9 (8%) developing symptomatic SN.

KEYWORDS
active TB, antiretroviral therapy, HIV, sensory neuropathy, tenofovir

1 | INTRODUCTION

The prevalence of HIV infection is high in sub-Saharan Africa and is expected to stay high for the foreseeable future[1] The high prevalence of HIV infections persists despite reduced infection rates because of the wide-spread availability of combination antiretroviral therapies (cART), which improve survival.[2] But this improved survival means that the total burden of chronic complications of HIV infection may

increase, and therefore, these complications need to be monitored and managed to mitigate the impact they may have on the lives of people living decades with HIV.[3,4]

One of the most common chronic neurological complications of HIV-infection and its treatment with neurotoxic combination antiretroviral therapy (cART) is sensory neuropathy (SN). The neuropathy is often symptomatic, with pain being the salient feature,[5,6] and these symptoms have a detrimental impact on quality of life and function.[6,7] Unfortunately, there are no widely-available pharmacological therapies with proven efficacy in the management of painful HIV-associated sensory neuropathy (HIV-SN),[8-10] which means that prevention of symptomatic SN is a key strategy. To limit side effects such as SN, the World Health Organization (WHO) firstly lowered the dose, and then removed, the neurotoxic antiretroviral drug stavudine from all first-line cART regimens globally.[11,12] With the worldwide elimination of stavudine in all first-line regimens and its replacement with tenofovir (TDF), an agent with no known neurotoxicity, together with earlier initiation of cART, it has been anticipated that the incidence of SN will decrease.

Several African studies have investigated the incidence of HIV-SN and factors associated with its development.[13-20] However, none of these studies assessed the incidence of SN in a cohort where all individuals were exposed only to TDF-based cART. Instead, these studies included individuals who had been exposed to several ART regimens (including stavudine) or who were on cART regimens that did not include TDF (globally, the most common cART initiation regimen). Furthermore, the assessments used within these studies to assess SN status are methodologically questionable. For example, one study only assessed symptoms,[15] while other studies did not state the method used to screen for SN.[13,14,17]

Consequently, we investigated the 6-month incidence of SN, using methods recommended for the assessment and grading of peripheral neuropathy for research and clinical purposes,[21-23] in ART naive South African people living with HIV/AIDS (PLWHA) and who were initiating TDF-based cART. We investigated the 6-month period after starting cART because on older stavudine-based cART, the neuropathy typically developed soon after starting therapy. As a secondary objective, we also described the clinical, disease-related and demographic risk factors associated with SN development in this cohort.

2 | METHODS AND MATERIALS

We approached all treatment-naïve adult PLWHA who were initiating TDF-based cART at the Lenasia South Community Health Hospital, Johannesburg, South Africa, to partake in the study. Recruitment was conducted from January 2016 to December 2016. Participants were followed up for a period of ~6-months. Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa, clearance number: M121018. Written, informed consent was obtained from all participants. An interpreter fluent in English and six indigenous languages explained the study rationale and procedures in the participant's language of choice.

3 | STUDY INCLUSION CRITERIA

All study participants had to be ≥18 years of age, have a confirmed HIV diagnosis, have never received any antiretroviral treatment (including monotherapy) for their HIV infection, be initiating TDF-based cART, and be free of signs of distal symmetrical polyneuropathy (see neurological assessment below), although isolated lower limb symptoms were permitted.

4 | STUDY EXCLUSION CRITERIA

We excluded all participants who did not meet the inclusion criteria, and/or who had the presence of medical conditions that affected sensation in, or assessment of, the feet and lower limbs (eg, Kaposi's sarcoma).

Eligible participants had the following demographic and anthropometric data recorded: sex, age, height, weight, ethnicity, and date tested positive for HIV infection, other potential risk factors for neuropathy (diabetes, alcohol consumption, vitamin B_{12} deficiency, diabetes mellitus, and treatment for active TB disease).

Treatment for individuals with active TB in South Africa is given in the form of Rifafour tablets. Rifafour tablets consist of R-rifampicin (150 mg), H-isoniazid (75 mg), Z-pyrazinamide (400 mg), and E-ethambutol (275 mg). Treatment with Rifafour tablets are weight based, so participants receive their amount of Rifafour tablets based on their weight. In accordance with South African National TB Guidelines for adults, isoniazid (INH) dosing in the treatment of both latent and active TB is weight based, with a daily dose of approximately 5 mg/kg/day, up to a maximum daily dose of 300 mg. All those treated with isoniazid were also given pyridoxine at a dose of at least 25-75 mg per day to reduce the risk of isoniazid-neuropathy.

The following laboratory data (where available) were obtained from participants medical records: CD4 T-cell count at the time of HIV testing (baseline CD4 T-cell count), current CD4 T-cell count (could be the same at baseline CD4 T-cell count), HIV viral load, current Hepatitis B infection, and current syphilis infection. A venous blood sample was taken from each participant at each visit to assess HBA1c percentage (HBA1c > 7% was used to define the presence of diabetes mellitus) and vitamin B12 concentrations (vitamin B12 < 142 pmol/L was used to define clinically relevant deficiency).

5 | PROCEDURES

5.1 | Neurological assessment

Participants were assessed for the presence of peripheral SN using an amended version of the brief peripheral neuropathy screen (BPNS), which included the original BPNS plus the assessment of sensitivity to

pin-prick. In its original format, the BPNS is a validated screening tool for HIV-SN,[24] and has been previously used in the South African population.[25,26] The BPNS case definition is for symptomatic HIV-SN and requires the bilateral presence of at least one symptom (pain/burning, paraesthesias, and numbness), and the bilateral presence of one clinical sign (vibration sense in great toe and ankle reflex testing). We added the assessment of pin-prick sensitivity, to the BPNS tool for the following reasons: (a) the two tests in the BPNS assess large fiber pathology, while pin-prick sensitivity assesses small-fiber pathology, (b) pin-prick sensitivity has high specificity in the detection of SN,[27] and (c) we wished to the increase the specificity of the assessment (at the cost of sensitivity) by increasing the number of bilateral clinical signs required by our case definition to two signs (see case definitions below).

A diagnosis of *symptomatic* SN was made based on the bilateral presence of at least two signs (decreased vibration sense in the great toe, absent ankle reflex, or decreased pin-prick sensitivity) and one symptom (pain, paraesthesias, or numbness) in the feet. A diagnosis of *asymptomatic* SN was made based on the bilateral presence of at least two signs, but no symptoms, in the feet. By using participants medical history, symptomatology, clinical assessment of nerve function, and the anatomical distribution of signs and symptoms, we met the recommendations of England and colleagues,[21] Haanpaa and colleagues,[22] and achieved a diagnostic certainty (for symptomatic SN) of "probable neuropathic pain" based on the grading criteria of Finnerup and colleagues.[23]

Vibration sense was assessed using a 128 Hz tuning fork on the distal interphalangeal joint of the participant's great toe. Vibration sense was recorded in both feet, with a recording of 10 seconds or less deemed abnormal.[24] Ankle reflexes were assessed using a rubber reflex hammer, where the investigator firmly struck the achilles tendon to elicit a response. A positive ankle reflex response was indicated by the plantar flexion of the foot and a negative response was recorded when there was no flexion of the foot. The reflex test was performed three times to confirm the response. Pin-prick sensitivity was assessed using a size four "single use" safety pin. The "sharp" and "blunt" ends of the safety pin were alternately placed on the dorsal surface of the participants great toes, and participants were asked to identify the sensation experienced as either "sharp" or "blunt." Identification of the "sharp" stimulus as being "blunt" or that it was not felt at all was deemed abnormal. If participants gave an incorrect answer, we then tested lateral to the point and then progressed proximally in order to identify the extent/borders of nerve dysfunction.

When symptoms were present, the anatomical distribution of the symptom(s) was(were) recorded and participants were asked to rate the severity of the symptom(s) on an 11-point numerical pain rating scale (NRS), anchored at 0 (no symptom experienced) to 10 (worst pain/or sensation imaginable). Participants were asked to rate their current level of pain (actual pain) and how long they have been experiencing this pain, that is, when did they start experiencing their pain.

6 | BLOOD SAMPLES

One blood sample (4 mL EDTA tube) was drawn from each at baseline and at every scheduled visit. Samples were analyzed for CD4 T-cell count, HIV viral load, HbA1c levels, and Vitamin B12 levels.

7 | TIMING OF FOLLOW-UP

Study participants were recruited over about a 6-month period, and each participant was followed up for 6 months, with four scheduled visits with the investigator. Following recruitment and consent procedures, visits were scheduled at 0 months (Baseline; day of treatment initiation), 2 weeks, 2-, 4-, and 6-months after starting cART (Figure S2). Participants were contacted telephonically a few days prior to their scheduled return to the hospital to confirm their appointment day and to remind them to meet with the investigator.

8 | STATISTICAL ANALYSIS

All analysis scripts and the outputs from the scripts can be accessed on Figshare (temporary link: https://figshare.com/s/a6f7923c973d200b850e, reserved doi: 10.6084/m9.figshare.7856660), or can be cloned from GitHub (https://github.com/kamermanpr/hivsn-incidence.git).

Descriptive statistics are presented as mean (SD) for parametric data, median (interquartile range, IQR) for nonparametric data, and percentages for frequency data. About 95% confidence intervals of the mean/median difference and odds ratios between "SN-free" individuals and individuals with SN were computed for analysis of factors associated with SN across the study period.

Our primary objective was to determine the incidence of SN. We used both cumulative incidence data and incidence rate data to determine the incidence of SN in our cohort. We first determined cumulative incidence, which measures the number of new cases per person in the population over a defined period of time (ie, a fixed follow-up period). Therefore, to calculate cumulative incidence we defined a fixed 6-month follow-up period. We also subdivided this period into a first and second, and 3-month period of this follow-up. To standardize the periods of follow-up, we cleaned the data and used only visits that fell into the indicated periods: (0-3 months), (3-6 months) and (0-6 months) to define SN status. Using this method, participant's whose last clinic visit occurred after 91 days (end of first 3-month interval) or at 182 days (end of 6-month interval), and who were found to have new-onset SN at this visit, were recorded as "SN-free" over the 3 or 6-month period of follow-up, respectively. This conservative strategy may have led to some under-estimation of the cumulative incidence of SN. We also determined incidence rate, which is a measure of the number of new cases per unit of time. We did not have exact dates of SN onset to define the per patient unit of time, and nor was there uniform spacing between clinic visits. Therefore, we chose to calculate an approximate SN onset time, arbitrarily defined as the number of days between the first neuropathy screening and the mid-

point between the visit when neuropathy was detected and the preceding visit. For participants who did not develop SN, the date of censoring was defined by the number of days between the first neuropathy screening and the last screening (study exit).

Our secondary objective was to determine possible risk factors for developing SN in our cohort. We first carried out an exploratory analysis using Cox proportional hazard models; however, various predictors violated assumptions of the model (eg, proportional hazard, linearity, no influence points). We therefore performed multivariable logistic regression analysis with elastic net regularization for variable selection, with visit 1 (baseline) characteristics as predictors of SN onset. Elastic net regularization performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the statistical model it produces. The process involved performing a 10-fold cross-validation to find the optimal lambda (penalization parameter) and thereafter running the analysis and extracting the model based on the best *lambda*. The advantages of regularized regression methods come at the cost of biased estimates, and so we have not reported the odds ratios. The models included the baseline values of all variables, except diabetes mellitus (as no participants had diabetes at baseline), Vitamin B_{12} deficiency (as only one person had a deficiency at baseline), and weight as it was co-linear with height.

9 | RESULTS

From January 2016 through to December 2016, 151 confirmed HIV-positive individuals were assessed for eligibility for the study. One hundred and twenty individuals met the requirements for inclusion in the study (Figure 1). Of the individuals not fulfilling the entry criteria,

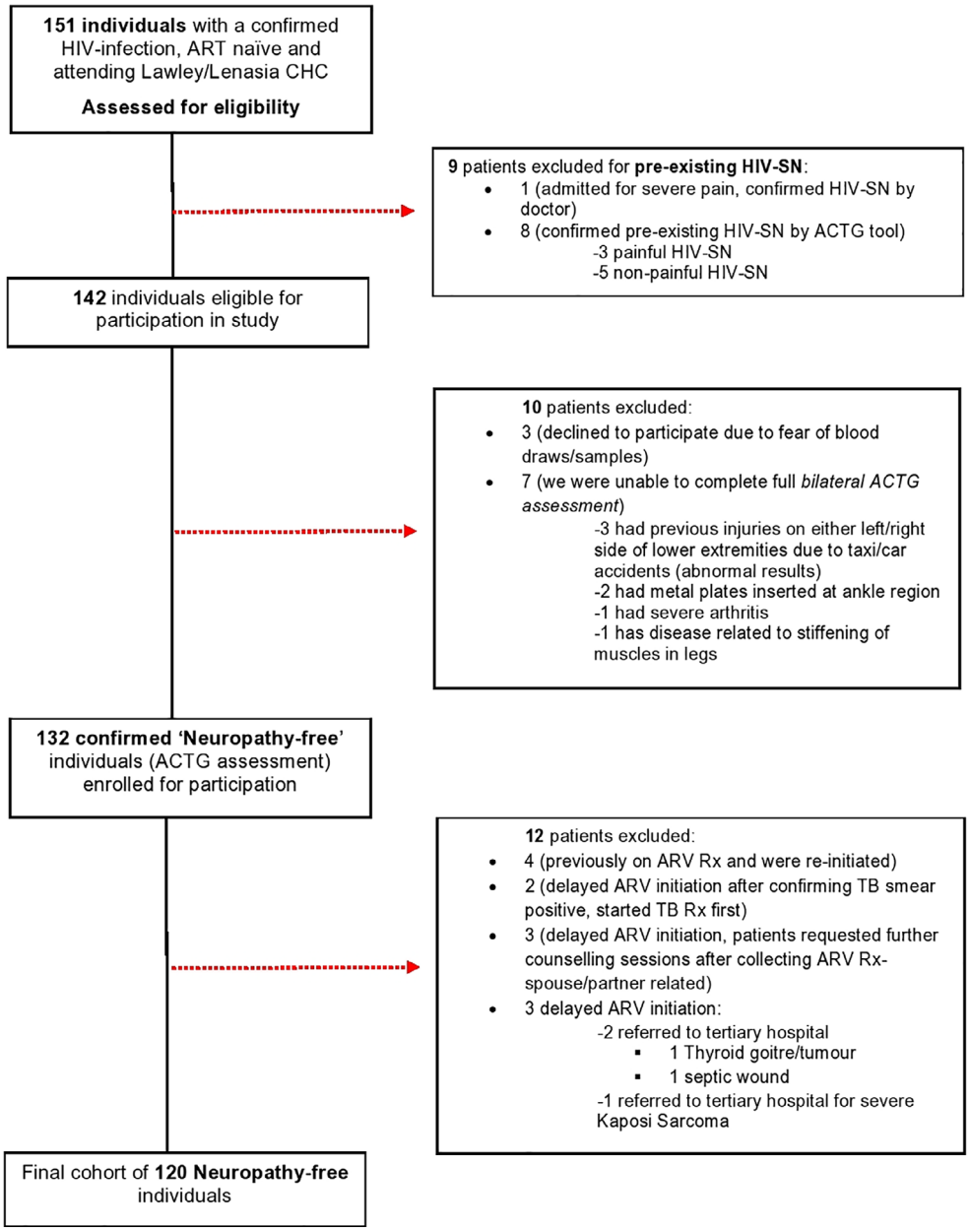


FIGURE 1 Flow diagram summarizing participant recruitment and exclusion

and so not recruited, nine (6%, 9/151) had a pre-existing neuropathy. All study participants identified themselves as of black African ancestry; 104 (87%) were South African.

10 | DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Baseline demographic and clinical characteristics of the study cohort are shown in Table 1. Over three quarters of the cohort were categorized under WHO stage III and IV (92/120, 77%), indicating that the majority of our patients were immunocompromised. The median (range) CD4 T-cell count at initiation of the study was 228 (1-1347) cells/μL. No participants had ever previously been exposed to any other antiretroviral therapy, and all participants were initiated on TDF-based fixed-dose triple combination (tenofovir + emtricitabine + efavirenz [TDF + FTC + EFV]). One-sixth of participants (20/120, 17%) were currently being treated for active TB disease with Rifafour with pyridoxine (vitamin B6) prophylaxis. About one third of participants (41/120, 34%) without a diagnosis of active TB disease (latent TB) were being treated prophylactically with INH and pyridoxine.

TABLE 1 Demographic and clinical characteristics of the study cohort at baseline (n = 120)

Characteristic	Entire cohort (n = 120)
Female Sex, n (%)	66 (55)
Age (years)	39 (12)
Height (m)	1.63 (0.08)
Weight (kg)	65.0 (15)
Current CD4 T-cell count (cells/μL)	228 (1–1347)
log_{10} viral load (copies/mL)	3.19 (1.69-6.5)
WHO staging, n (%)	
I	13 (11)
II	15 (12.5)
II	37 (31)
IIV	55 (46)
Starting cART regimen, n (%):	
TDF-based	120 (100)
Non TDF-based	0 (0)
Active TB disease, n (%)	20 (17)
Standard units of alcohol consumed (units/week)	15.0 (3-90)
Initial Vitamin B_{12} level (pmol/L)	316.5 (140-693)
Vitamin B_{12} deficiency, n (%)	1 (1)
Current hepatitis B infection, n (%)	4 (3)
Current syphilis infection, n (%)	3 (3)
Initial HbA1c percentage	5.4 (4.0-7.0)
HbA1c > 7%, n (%)	1 (1)
Language group, n (%)	
isiZulu	45 (38)
isiXhosa	20 (17)
Sesotho	26 (22)
Setswana	7 (6)
Other	22 (18)[a]

Note: Dichotomous variables are presented as number (%), normally distributed continuous variables are presented as mean (standard deviation) and non-normally distributed continuous variables are presented as median (range).
[a]Other, n (%); Tsonga, 2 (2); Venda, 2 (2); Pedi, 3 (3); Afrikaans, 3 (3), Portuguese 7 (6), Chewa 4 (3), Shona 1 (1).

11 | SYMPTOM PREVALENCE AT BASELINE

At baseline, 20% of participants (24/120) presented with pain, 14% (17/120) had paraesthesias, and 5% (6/120) presented with numbness in the lower limbs. Despite the presence of these symptoms they were all classified as "neuropathy-free," as none of these participants presented with any signs of SN. Symptoms were located primarily in the foot region for 85% (40/47) of participants with symptoms, with the remaining 15% (7/47) of participants experiencing the extension of these symptoms up to the ankle and knee regions. In participants with pain, the median pain intensity was five (IQR 2-10) on an 11-point numerical pain rating scale.

12 | PATIENT FOLLOW-UP

Of the cohort, 88% had at least three clinic visits and we had a study retention rate of 69%. Although participant follow-up was planned for 0 (the day of cART initiation), 2, 4, and 6-months of cART, there was variability in the visit schedules of participants as depicted in (-Figure S3). Timing of clinic visits stratified according to SN status is provided in Figure 2.

The median (IQR) number of clinic visits for the entire cohort (n = 120) was three (3) (Figure S4). There was no difference in the number of clinic visits between those individuals that remained "SN-free" (median [IQR]:[3]) and those that developed SN (3 [3-3.25]); X^2 (*df*:1) = 4.35, *P* = .2]. There was also no difference in the number of days between the first and last clinic visit between those individuals that remained "SN-free" (median [IQR] 184 [133-199]) and those that developed SN (195 [182-208]), (Z = −2.10, *P* = .03; two sample van der Waerden test) (Figure S5), or days between successive visits (F [1] = 0.02, *P* = 0.87; Type II Wald F test with Kenward-Roger df) (Figure S6).

13 | INCIDENCE OF NEUROPATHY

Of the 120 confirmed "SN-free" patients who were enrolled at baseline, a total of 31% (37/120) of patients were lost to follow-up by the 6-month study period. However, 88% (105/120) completed at least three visits or more. A total of 17% (20/120) developed SN and 83% (100/120) remained "SN-free" (Figure S1). Using these data, we calculated the cumulative 6-month incidence of SN to be 140 cases per 1000 patients (95% CI: 80-210). The cumulative incidence over the first 3-months of follow-up was 60 cases per 1000 patients (95% CI: 20-100), and for the second 3-months of follow-up was 90 cases per

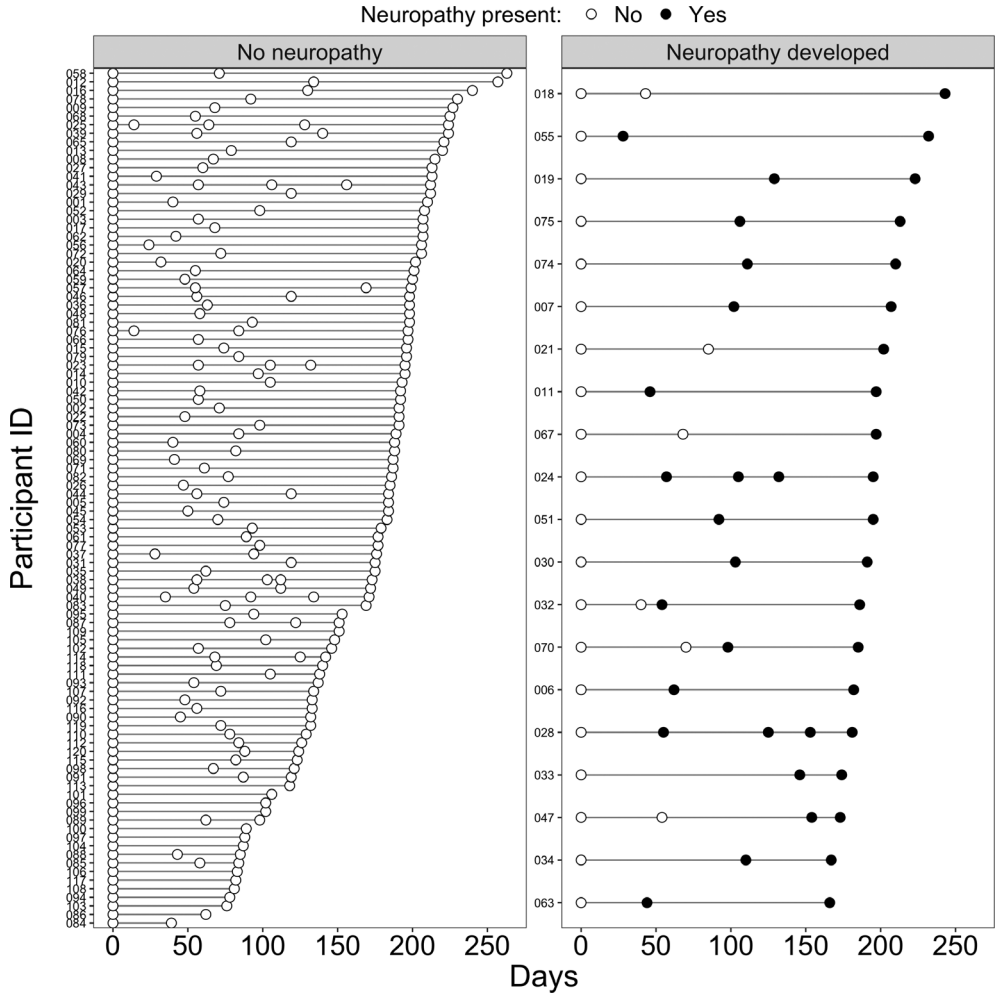


FIGURE 2 Timing of clinic visits for the entire cohort, stratified according to the development of SN. Open circles show visits where participants were "SN-free," while closed circles show visits where participant were identified as having developed SN. SN, sensory neuropathy

1000 patients (95% CI: 40-140). The incidence rate of SN was 0.37 (95% CI: 0.2-0.5) per person-year. Nine (8%) individuals developed symptomatic SN and 11 (9%) individuals developed asymptomatic SN.

The presence of symptoms at baseline (including pain, paraesthesias, numbness, and burning) were associated with an increased risk of development of SN across the 6-month period (X^2 [*df*:1] = 15.09, $P < .001$). Of the (47/120, 39%) of participants that had presented with symptoms at baseline, 13% (6/47) developed symptomatic SN and 9% (4/47) developed asymptomatic SN. The median pain intensity of the 15% (3/20) patients that developed symptomatic SN in the first 3-month period, was four (IQR: 3-5). The median pain intensity of the 30% (6/20) patients that developed symptomatic SN in the second 3-month period, was 5 (IQR: 4-10).

14 | SURVIVAL CURVE ANALYSIS

Figure 3 shows the Kaplan-Meier survival curve with the number and percentage of patients at risk for developing neuropathy across the study period. Of the 20 individuals that developed neuropathy, 7% (8/120) of patients developed neuropathy within the first 50 days of cART; one patient developed neuropathy at about 2 weeks. Within the next 100 days of cART, 10% (12/120) individuals developed neuropathy. The last event of neuropathy development occurred at about

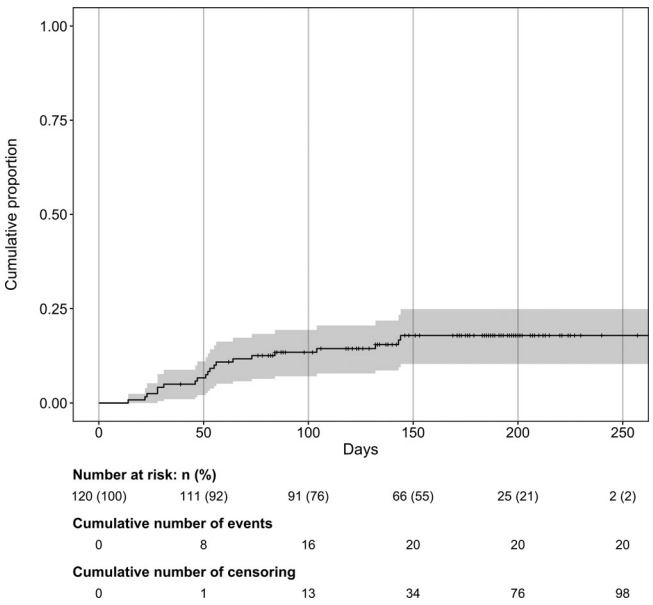


FIGURE 3 Kaplan–Meier survival curve showing the number and percentage of participants at risk for developing neuropathy across the study period

TABLE 2 Elastic net variable selection

	Alpha[a]			
	0.125	0.216	0.343	1.0
Age (years)	+	+		
Female sex (yes)				
Height (m)	+	+	+	+
CD4 (cells/μl)				
Viral load (copies/ml)				
Alcohol (units/week)	+			
TB current (yes)	+	+	+	+
Rifafour[b]/INH[c] (yes)				

Note: The results of all univariate analyses can be found in Figures S8 to S14.
Abbreviation: TB, tuberculosis.
[a]Alpha is the mixing parameter between L2 (ridge) and L1 (lasso) regularization.
[b]Participants with active TB disease received rifafour plus pyridoxine prophylaxis.
[c]Participants without active TB disease received isoniazid and pyridoxine, purely as prophylactic treatment.

140 days. A secondary Kaplan-Meier survival analysis of whether the onset of neuropathy differed between those who developed a painful neuropathy compared to those with an asymptomatic neuropathy found that the onset of painful neuropathy was more rapid than the onset of asymptomatic neuropathy (X^2 [df:1] = 13.4, $P < .001$; Figure S7). The first painful neuropathy occurred at ± 2 weeks. The development of asymptomatic peripheral sensory neuropathy had a slightly delayed onset with the first asymptomatic neuropathy occurring at about day 25.

15 | MULTIVARIABLE ANALYSIS

We included baseline clinical, demographic, and physical factors in the modeling process. The full model included: sex, active TB disease, age, Rifafour/INH prophylaxis treatment, CD4 T-cell count, height, viral load, and alcohol consumption. Across all alphas, and the optimal lambda at each alpha (Table 2), the models repeatedly returned only two variables: height and active TB disease.

16 | DISCUSSION

We investigated the 6-month incidence of SN in a cohort of PLWHA of black African ancestry who were all exposed to TDF-based cART. We report a 6-month cumulative incidence of SN of 140 cases per 1000 patients (95% CI: 80-210). The incidence rate was 0.37 (95% CI: 0.2-0.5) per person year. A roughly equal number of individuals developed symptomatic (8%, 9/120) vs asymptomatic (9%, 11/120) SN. The presence of neuropathic pain was associated with a more rapid onset of symptomatic SN. Height and having current active TB disease were the only consistent independent predictors of SN in the cohort across several modeling parameters.

Our findings are novel and provide the first incidence data for individuals exposed to TDF-based cART. Our findings indicate that the number of new cases of SN is still high, even if substantially lower than those observed in a similar cohort initiating stavudine-based cART.[28] In the previously mentioned cohort, 44 individuals initiated stavudine-based therapy, and 41% (18/44) of these individuals developed SN within 6-months.[28] Our findings in the era of TDF-based cART highlight two key facts: (a) Incidence of SN is lower on TDF-based cART, but still higher than we anticipated based on the lack of neurotoxicity of these drugs, and (b) SN in the TDF-based era tends to present asymptomatically more often compared to stavudine-based therapy where symptomatic SN was more prevalent (~61%).[28]

While the increase in the proportion with asymptomatic neuropathy is welcomed, this finding needs to be regarded with some caution: we only followed individuals for 6 months and so it is not clear if asymptomatic SN remained asymptomatic or whether it may have progressed to being symptomatic. Indeed, one high-quality study suggested that asymptomatic SN may transition into symptomatic SN within a 12 to 24-month period on cART.[29] When symptomatic neuropathies developed within our cohort, they developed rapidly (most cases occurring within 3-months of initiating cART, and as early as 2 weeks), compared to asymptomatic neuropathies, which developed more slowly (most cases within ± 5-months of initiating cART). Rapid onset, painful neuropathies have also been reported in cohorts on other cART regimens including stavudine, zidovudine, and zalcitabine.[30]

The data regarding associations between SN and disease markers such as CD4 T-cell count and viral load are equivocal.[31-33] Indeed, we found no association with these variables and SN. However, a role for immune dysfunction in mediating SN cannot be excluded. For example, animal models of HIV and ART-induced neuropathy show immune activation in the dorsal root ganglia and nerve trunks, and these changes mimic those seen in postmortem studies in humans with HIV-SN (for review Reference 34: Moreover, there are preliminary data suggesting a particular inflammatory profile may be responsible for neuropathy, and particularly, rapid onset painful neuropathy. In individuals starting cART, patients with greater interleukin-1-receptor (IL-1R)-antagonist levels at baseline, and 2 weeks later elevated levels of soluble interleukin-2 receptor-alpha and tumor necrosis factor (TNF) receptor-II were more likely to develop a symptomatic SN.[19] Thus, it is possible that a particular inflammatory response results in a faster onset and painful SN, rather than exposure to a particular ART-regimen. Future studies are required to compare inflammatory profiles between those developing fast and slow onset SN.

The presence of active TB disease was an independent predictor of SN in our cohort. Importantly, there was no association found between Rifafour exposure and SN, in our setting. The association between SN and treatment for active TB disease is well documented on stavudine-based regimens, even with pyridoxine supplementation.[18,25,35-37] However, our study is the first study to associate TDF-based cART and confirmed active TB disease with the development of SN. The association between active TB disease and SN in those

individuals starting ART, may not be specific to the type of ART, therefore, but perhaps related to the timing of ART and concurrent active TB disease. The timing of ART initiation in the face of active TB disease can lead to TB-immune reconstitution inflammatory syndrome (IRIS). This condition involves a strong inflammatory response to TB antigens during the acute phase of immune system reconstitution that leads to clinical deterioration.[38] If such immune dysregulation also is associated with immune activation in peripheral nerves, then the probability of clinically apparent neuropathy would increase. However, none of our participants developed frank TB-IRIS, so this cannot be the mechanism underlying this association. Instead, we hypothesize concurrent active TB disease may reduce the decrease in inflammation that typifies the initiation of cART,[39] thus predisposing affected individuals to develop a neuropathy. Whatever the mechanism, if the relationship between SN, concurrent active TB disease and cART is causal, then SN will remain a problem in countries with high co-infection rates despite the introduction of non-neurotoxic regimens.

Height was an independent predictor of SN in our cohort. Height is a well-established risk factor for length-dependent polyneuropathies such as SN and diabetic sensory polyneuropathy.[40] Therefore, it is not surprising that taller individuals would be more susceptible to the development of SN.[41] However, there may have been an interaction between height, weight and dose of isoniazid exposure. That is, height was correlated to weight, and weight is a determining factor in Rifafour (which contains isoniazid) dose.

There are several limitations to our work. One of these limitations was the sample size of our cohort. We aimed to recruit a sample size of n = 150 individuals, although we did not achieve this number of participants, our cohort still consists of the largest study of SN in ART naïve individuals initiating TDF-based cART. Our sample size was a direct result of the referral of ART naïve individuals to larger tertiary-based hospitals when they presented to the local clinic (where our recruitment was based) with existing opportunistic infections such as cryptococcal meningitis, pneumonia, and Kaposi's sarcoma. These opportunistic infections are better managed in these large tertiary hospitals, due to the availability of specialist care. Such individuals were initiated on ART at these tertiary hospitals and they typically did not return to their local clinic, thereby reducing the number of ART naïve individuals available at site for study recruitment. It also meant that our cohort represented uncomplicated cases of HIV infection, and our results cannot be extrapolated to more complicated cases. The other limitation was our retention of participants. We aimed to retain as many study participants as possible across the six-month period of our study. Despite having specific times for patient visits on our protocol and allowing ±2 weeks before or after scheduled visits for patients to come in for their follow up visits, we faced several issues at the research site which were out of our control and which disrupted the timing of participants returning for follow-up visits. These issues included frequent community service delivery protests at our research site, which were violent and resulted in all entrances to the hospital being blocked.

An additional limitation was not using a nerve conduction study (NCS) to confirm the neuropathy or other techniques to investigate the impairment of small nerve fibers. This study was conducted in a resource limited clinical setting and we did not have access to NCS equipment or a specialist clinician to assist with NCS testing thus this option was not possible. Therefore, we added the assessment of pin-prick sensitivity, to the BPNS tool for the following reasons: (a) the two tests in the BPNS assess large fiber pathology, while pin-prick sensitivity assesses small-fiber pathology, (b) pin-prick sensitivity has high specificity in the detection of toxic SN,[27] and (c) we wanted to the increase the specificity of the assessment (at the cost of sensitivity) by increasing the number of bilateral clinical signs required by our case definition to two signs (decreased pin-prick sensitivity, absent ankle reflexes or decreased vibration sense in the big toe). Thus, we are confident to have assessed at clinical level both large and small fiber pathology in our cohort.

We report that the incidence of SN on TDF-based cART, based on clinical evaluation, is lower than that observed on stavudine-based therapies, and that it is more frequently asymptomatic. Nevertheless, a percentage of individuals developed a rapid onset symptomatic neuropathy, which might lead to disability and reduced quality of life.[42] Concomitant active TB disease increased the risk of developing SN. Our findings suggest that SN continues to be a clinical problem in low-income countries where prevalence of comorbid TB and HIV remains high.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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