



## Effect of Stavudine-Based Antiretroviral Therapy on the Severity of Polyneuropathy in HIV/AIDS Patients: A Preliminary Report From Zaria, Northern Nigeria

*Effet de la Stavudine-traitement antirétroviral à base de la gravité de Polynévrite au cours de lutte contre le VIH / SIDA patients: un rapport préliminaire de Zaria, au Nigeria du Nord*

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### ABSTRACT

**BACKGROUND:** Stavudine, a nucleoside reverse transcriptase inhibitor, used as first-line antiretroviral drug in many developing countries is said to exacerbate distal symmetrical polyneuropathy in HIV/AIDS patients.

**OBJECTIVE:** To evaluate the severity of distal symmetrical polyneuropathy in HIV/AIDS patients on stavudine-based antiretroviral therapy.

**METHODS:** Two hundred and twenty consecutive HIV-infected antiretroviral-naïve adults who were eligible for antiretroviral therapy were studied. Each patient was evaluated using a questionnaire, which contained bio-data and distal neurologic symptoms/signs adapted from the subjective peripheral neuropathy screen and the Leeds assessment of neuropathic symptoms and signs pain score. Patients were then put on stavudine, lamivudine and nevirapine. For three months, after which each patient was re-evaluated using the same protocol. Patients with other risk factors for distal symmetrical polyneuropathy were excluded from the study.

**RESULTS:** Three months of antiretroviral therapy reduced the mean neuropathic symptoms and signs scores from  $0.71 \pm 0.76$  to  $0.26 \pm 0.47$  ( $P=0.00$ ) and  $0.72 \pm 0.57$  to  $0.58 \pm 0.55$  ( $P=0.00$ ) respectively. The number of patients with symptoms and signs also reduced from 97.8% to 24.4% and 65.9% to 55.0% respectively while the mean CD4+ count rose from  $194.3 \pm 80.4$  cells per  $\mu\text{L}$  to  $416.1 \pm 191.2$  cells per  $\mu\text{L}$  of blood.

**CONCLUSION:** Three months of stavudine-based antiretroviral therapy reduces the severity of distal symmetrical neuropathy in HIV/AIDS patients, but more studies are needed to evaluate the long-term neuropathic effect of stavudine on Africans. *WAJM 2011; 30(5): 354–358.*

**Keywords:** Antiretroviral therapy, distal symmetrical polyneuropathy, HIV/AIDS, nucleoside reverse transcriptase inhibitors, stavudine.

### RÉSUMÉ

**CONTEXTE:** La stavudine, un inhibiteur de la transcriptase inverse nucléoside, utilisé comme première ligne de traitement antirétroviral dans de nombreux pays en développement est dit à exacerber distale polyneuropathie symétrique patients VIH / SIDA.

**OBJECTIF:** Pour évaluer la gravité de la polyneuropathie symétrique distale patients VIH / SIDA sur la stavudine à base de thérapie antirétrovirale.

**MÉTHODES:** Deux cent vingt consécutifs infectés par le VIH adultes naïfs de traitement antirétroviral qui étaient admissibles à la thérapie antirétrovirale ont été étudiés. Chaque patient a été évaluée à l'aide d'un questionnaire, qui contenait des données bio-et distale des symptômes neurologiques ou signes adaptés à l'écran une neuropathie périphérique et l'évaluation subjective des symptômes neuropathiques Leeds et le score de la douleur des signes. Les patients ont ensuite été mis sur la stavudine, lamivudine et névirapine. Pendant trois mois, après quoi chaque patient a été réévalué en utilisant le même protocole. Les patients présentant des facteurs de risque et d'autres pour polyneuropathie symétrique distale ont été exclus de l'étude.

**RÉSULTATS:** Trois mois de la thérapie antirétrovirale réduit les symptômes neuropathiques moyennes et les scores des signes de  $0,71 \pm 0,76$  à  $0,26 \pm 0,47$  ( $P = 0,00$ ) et  $0,72 \pm 0,57$  à  $0,58 \pm 0,55$  ( $p = 0,00$ ) respectivement. Le nombre de patients présentant des symptômes et des signes a également réduit de 97,8% à 24,4% et 65,9% à 55,0% respectivement, tandis que les CD4 + count moyennes est passé de  $194,3 \pm 80,4$  cellules par ml à  $416,1 \pm 191,2$  cellules par ml de sang.

**CONCLUSION:** Trois mois de la stavudine basée sur la thérapie antirétrovirale réduit la sévérité de la neuropathie symétrique distale patients VIH / SIDA, mais d'autres études sont nécessaires pour évaluer l'effet à long terme de la stavudine neuropathique sur les Africains. *WAJM 2011; 30(5): 354–358.*

**Mots-clés:** thérapie antirétrovirale, distale polyneuropathie symétrique, le VIH / sida, nucléosidiques de la transcriptase inverse, la stavudine

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Abbreviations: ATN, Antiretroviral toxic neuropathy; AZT, Zidovudine; DSP, Distal symmetrical polyneuropathy; TDF, Tenofovir.

## INTRODUCTION

Many studies have shown that 40–70% of patients living with HIV/AIDS present with neurological features<sup>1,2</sup> and 10–30% with peripheral neuropathy.<sup>3,4</sup> Peripheral neuropathy may be the presenting and only manifestation of HIV infection, with distal symmetrical polyneuropathy (DSP) as the most common form.<sup>3,4</sup> Distal symmetrical polyneuropathy which is pathologically evident in almost all patients who die of AIDS is a predominantly sensory neuropathy with mild motor features. Features range from excruciating pains to proprioceptive loss in a stock and glove distribution.<sup>3</sup> Similar in clinical features to DSP is antiretroviral toxic neuropathy (ATN) described in 5–24% of patients on the dideoxy-nucleoside reverse transcriptase inhibitors' (ddx-NRTIs) such as stavudine (d4T), didanosine (ddl), and zalcitabine (ddc).<sup>5</sup> Antiretroviral toxic neuropathy is said to be worse in patients with advanced HIV disease and previous history of peripheral neuropathy or those on treatment with a combination of two NRTIs and hydroxyurea.<sup>5,6</sup> Unlike DSP which is slowly progressive, ATN tends to evolve more rapidly, within a week to six months of therapy and usually resolves if the offending drug is withdrawn.<sup>5</sup>

The pathogenesis of DSP and/or ATN is incompletely understood. While DSP is thought to result from destructive interaction between nerve growth factor and pro-inflammatory chemokines and tumor necrosis factor released by HIV infected macrophages,<sup>7</sup> Antiretroviral toxic neuropathy is thought to be due to impairment of mammalian mitochondrial DNA polymerase gamma during cellular phosphorylation of the drugs to the active triphosphate.<sup>8</sup> Cases of biopsy-proven mitochondrial damage in patients with ATN have been reported.<sup>8</sup> Other investigators have suggested that ATN may be due to depletion of acetyl-L-carnitine which causes a disruption of mitochondrial metabolism with resultant toxic accumulation of fatty acids. This was because a comparison of the serum levels of acetyl-L-carnitine in HIV-infected patients taking the ddx-NRTIs found lower concentrations in patients

with peripheral neuropathy than those without neuropathy.<sup>9</sup>

In Europe<sup>10</sup> and the United States of America,<sup>11</sup> the first generation ddx-NRTIs have been withdrawn because of their long-term toxicities including ATN and, in 2006 the World Health Organization (WHO) recommended the gradual replacement of d4T as first-line drug with zidovudine (AZT) or tenofovir (TDF) for the same reason.<sup>12</sup> Because d4T is cheap and easily affordable by many sub-Saharan countries, it is still the backbone of first-line ART, particularly in conditions where AZT and TDF are not recommended. Because of paucity of data on ATN from Nigeria and other Sub-Saharan African countries, this research was undertaken to investigate the short-term effect of stavudine on the severity of distal symmetrical polyneuropathy in HIV/AIDS patients.

## SUBJECTS, MATERIALS, AND METHODS

### Study Period and Site

This research was a prospective study of adult HIV/AIDS patients who presented to the Global Fund assisted HIV clinic in Ahmadu Bello University Teaching Hospital (ABUTH), Shika, Zaria between August 2005 and May 2006.

The HIV clinic of the Department of Medicine, ABUTH, Shika-Zaria was part of the Global Fund pilot program on HIV/Tuberculosis in which 600 patients were expected to be treated with stavudine, lamivudine and nevirapine free of charge for one year in the first instance beginning from August, 2005. The hospital is a referral centre for Kaduna State, as well as other states in the Northwestern and Northcentral geopolitical zones of Nigeria.

### Study population

**Sample Size Calculation:** This was determined from the formula,<sup>13</sup>

$$N = Z^2 P (1 - P) / d^2, \text{ where}$$

N = desired sample when population is greater than 10, 0000.

Z = confidence interval at 95% (1.96)

P = prevalence rate of HIV infection in Kaduna State = (7.9%),<sup>14</sup>

d = sampling error at 0.05.

This gave a sample size of 112 but because of referrals or losses, a sample

size of 220 patients was chosen as the study population.

### Patient Selection

- i. **Inclusion Criteria:** Adult patients, males and females, 18 years and above with laboratory evidence of HIV infection (positive antibodies to HIV-1/HIV-2 confirmed by Western blot), CD4 cell counts of less than 350 cells/mm<sup>3</sup>, and without previous history of anti-retroviral therapy (ART-naïve).
- ii. **Exclusion Criteria:** Patients with risk factors for DSP such as diabetes mellitus, malnutrition, vitamins deficiencies, peripheral vascular disease, connective tissue disease, chronic liver and renal diseases, thyroid dysfunctions, positive VDRL test, history of chronic alcohol ingestion or ingestion of drugs such as metronidazole, dapson, isoniazid, nitrofurantoin, chloramphenicol, chloroquine, gold, hydralazine, cytotoxics, phenytoin, pyridoxine and ethambutol. Also excluded were patients known to be exposed to paints, laboratory chemicals, radiographic and photographic materials.

### Data Collection

A screening instrument adapted from the subjective peripheral neuropathy screen<sup>15</sup> and the Leeds Assessment of Neuropathic Symptoms and Signs<sup>16</sup> was administered on each patient after interpretation of the severity scores to the patients (Table 1). The results of CD4+ cell counts, full blood cell counts, liver function tests and other ancillary investigations were documented.

### Clinical Management and Patients Follow-up

After clinical evaluation, eligible patients were placed on oral nevirapine 200mg daily, lamivudine 150mg twice daily and stavudine 40mg twice daily. This regimen was continued for two weeks after which the dose of nevirapine was increased to twice daily. The patients were re-evaluated every four weeks, and at each visit, appropriate information was obtained on adverse drug events, drug adherence and presence of opportunistic

infections, and these were treated accordingly.

At the 12th week, patients' CD4+ and full blood cell counts were re-evaluated. Those patients who had taken more than 95% of their drugs between clinic visits and were considered to be adherent<sup>17</sup> were re-evaluated using same baseline screening tool.

### Ethical Considerations

All major ethical considerations were put in place before and during the study. The study was approved by the Institution Review Board and the Research Ethics Committee of Ahmadu Bello University Teaching (ABUTH) Zaria. Informed written consent was obtained from the patients after they were sufficiently counseled. Relevant confidentiality was maintained throughout the study period. Also, patients were given full information on the various drugs, their costs, possible side effects and the need for adherence and laboratory monitoring of CD4+ cell counts, full blood counts, hepatic and renal function, among others.

### Limitations of the Study

There were no facilities for plasma HIV viral load monitoring at the time of this study.

### Data Analysis

Data management and statistical analysis was done using the EFI INFO 6 statistical software. Relevant tables to the study objectives were constructed and appropriate statistical tests were used to investigate the significance of any relationship between variables. Means and standard deviation were used to describe continuous variables, and proportions were used for discontinuous or categorized data. The "t" test was used to compare means of two continuous variables, while the Pearson chi-square was used to determine the significance of association between proportions or groups. P values < 0.05 were considered statistically significant.

## RESULTS

### Demographic Characteristics

Two hundred and eleven (95.9%) of the patients were infected by HIV-1 while

the remaining nine (4.1%) had dual (HIV-1 and HIV-2) infection. Males were sixty-six (30.0%) in number while the females were 154 (70.0%) giving a male-to-female ratio of 1:2.3. The respective mean ages of the males and females were 38.9±8.1 and 33.5±7.62 years (p> 0.05). The age group 18–39 years formed 73.7% of the study population, followed by the age group 40–59 years (25.5%) and the elderly (>60 years) with 1%. The youngest patient, aged 18 years, was a spinster. The females were dominant in all the groups accounting for 154(70%) of the population, 67(30.5%) of them were married, 50(22.7%) were widows, 36(16.3%) single and 1(0.5%) was divorced. Fifty (22.7%) of the males were married, 14(6.4%) were single while 2 (0.9%) were widowers. There was no male divorcee. At 12 weeks of ART, 200 (91%) and 20 (9%) of the subjects had achieved adherence rates of 100% and 95% (defined as missing a dose of anti-retroviral drug in a month) respectively.

### Comparison of the Effect of ART on Distal Symmetrical Neuropathic Symptoms and Signs Score between HIV-1 and HIV-1 +HIV-2 Co-infected Patients

At baseline, dual HIV infected patients had higher mean neuropathic

symptoms score while HIV-1 infected patients had higher signs score. However, while ART significantly reduced the mean neuropathic symptoms score of all the subjects and the signs score of the HIV-1 infected patients respectively, it had no effect on the signs score of dual HIV-infected patients (Table 2).

### Effect of ART on Severity of Distal Neuropathic Symptoms and Signs

With ART, the mean neuropathic symptoms and signs decreased from 0.71±0.76 to 0.26±0.47 (t=8.053, P=0.00) and 0.72±0.57 to 0.58±0.55 (t=2.816, P=0.00) respectively. The proportion of patients with neuropathic symptoms decreased from 215 (97.8%) to 54 (24.5%) (p=0.02), and the proportion with no symptoms increased from 5 (2.2%) to 166 (75.5%) (P=0.00), while there was no significant reduction in the proportion of patients with signs (Table 3).

### Effect of ART on CD4+ Cell Count and Distal Symmetrical Neuropathic Symptoms and Signs

Before initiation of ART, patients with CD4+ cell counts ≥201/μl had significantly lower mean neuropathic symptoms scores (P<0.05) and

**Table 1: Interpretation of Symptoms and Signs Score**

Score	Symptom Severity	*Sensory	Motor
0	None (asymptomatic)	No abnormality	No abnormality
1	Very mild, occasionally present but no discomfort	Normal pain and vibration and reduced light touch to great toes	Grade 4/5 power, normal knee and reduced ankle reflexes (without re-enforcement)
2	Mild, always present but no discomfort	Reduced pain and vibration and loss of light touch to great toes	Grade 3/5 power, normal knee and reduced ankle reflexes (with re-enforcement)
3	Moderate discomfort with occasional disruptions of activities of daily living	Loss of all three modalities to great toes	Grade 2/5 power, reduced knee and absent ankle reflexes (with re-enforcement)
4	Severe discomfort with disruptions of activities of daily living	Loss of all three modalities to the level of ankles and/or to the dorsum of distal phalanges of thumbs	Grade 1/5 power, reduced knee and absent ankle reflexes (with re-enforcement)
5	Very severe and unpleasant causing total disruption of activities of daily living	Loss of all three modalities to the level of the knees and/or to the wrists	Zero power, absent knee and ankle reflexes (with re-enforcement)

\*Sign (deficit) severity: sensory (vibration, light touch and pain to dorsum of great toes)  
Motor (muscle power, deep tendon reflex)

**Table 2: Mean Symptoms Scores of HIV - Infected Patients**

Variable	Mean Score		All Patients
	HIV-1	HIV 1/2	
Number of Patients (%)	211(95.9)	9(4.1)	
N(%) with symptoms			
Before Therapy			215(97.8)
After Therapy			54(24.5)
Symptom Score			
Before ART	0.70±0.75	0.90±0.93*	
12 weeks of ART	0.25±0.46	0.22±0.67	
Signs			
Before ART	0.73±0.57*	0.44±0.53	
12 weeks of ART	0.58±0.55	0.44±0.53	

\*Significant difference,  $p < 0.01$ . Before and after therapy

**Table 3: Effect of Treatment on Signs and Symptoms**

Feature Before Treatment	At 12 Weeks	P value
HIV-1		
Symptoms		
Number (%) of Patients	211(95.9)	211(95.9)
Mean Symptom Score	0.70±0.75	0.25±0.4
Signs		
Mean Score	0.73±0.57	0.58±0.55 <0.01
HIV-1 + HIV-2		
Number (%)	9(4.1)	9(4.1)
Mean Symptoms Score	0.90±0.93	0.22±0.67 <0.01
Mean Sign Score	0.44±0.53	0.44±0.53 1.00
All Groups		
Symptoms [N(%)]	215(97.8%)	54(24.5) 0.02
N(%) Without Symptoms	5(2.2)	166(75.5) <0.01

**Table 4: Effect of ART on CD4+ Cell Count and Distal Neuropathic Symptoms and Signs**

No of Patients	CD4+ cell/ $\mu$ L	Mean Symptoms Score	P-value	Mean Signs Score	P-value
Before ART					
120(54.5)	$\leq 200$	0.84±0.82	0.00	0.77±0.53	0.17
100(45.5)	$\geq 201$	0.55±0.66		0.66±0.61	
12 weeks of ART					
23 (10.5)	$\leq 200$	0.43±0.59	0.05	0.65±0.65	0.48
197 (89.5)	$\geq 201$	0.24±0.45		0.57±0.54	

insignificantly lower sign scores ( $P > 0.05$ ) than those with counts  $\leq 200/\mu$ L. When ART was initiated, the mean CD4+ cell count rose from  $194.3 \pm 80.4/\mu$ L to  $416.1 \pm 191.2/\mu$ L, ( $p = 0.01$ ) thereby decreasing the number of patients with

CD4+ count  $\leq 200$  cells/ $\mu$ L from 120 (54.5%) to 23 (10.5%) and increasing the number with counts  $\geq 201$  cells/ $\mu$ L from 100 (45.5%) to 198 (89.5%) respectively, all at significant levels. Although the mean symptoms and signs scores were lower

in patients with CD4+ cell counts  $\geq 201/\mu$ L, the difference was not statistically significant ( $p > 0.05$ ) (Table 3).

## DISCUSSIONS

### Distribution of Patients by HIV Types

In this study, HIV-1 was the predominant cause of infection being responsible for 95.9% of the cases while the remaining 4.1% was due to dual HIV (1 and 2) infection. There was no lone HIV-2 infection. This is somewhat different from the result of the research conducted by National AIDS/STDs Control Programme (NASCP) which gave the distribution of HIV-subtype in Nigeria as follows: HIV-1 (87%), HIV-2 (7%) and HIV1+2 (6%).<sup>14</sup> Although patients with HIV-1 and HIV-2 co-infection were less than 5% in this study, they manifested more severe symptoms but lower neuropathic signs than the HIV-1 infected individuals. HIV-1 is known to present with earlier and more severe signs and symptoms than lone HIV-2,<sup>18</sup> and therefore it was not surprising that patients with dual HIV infection presented with more severe neuropathic symptoms. However the reason for our current finding of less severe signs could be due to the small number of HIV-1 and HIV-2 co-infected patients seen in this study.

### Effect of Antiretroviral Therapy on CD4+ Count and DSP

About 55% of the patients presented at the AIDS stage of the disease with a mean baseline CD4+ count of  $194.3 \pm 80.4/\mu$ L. It is therefore not surprising that more than 97% and 65% had neuropathic symptoms and signs respectively. This result agrees with many others which have shown an inverse relationship between the frequency and severity of DSP and CD4+ cell count.<sup>3,4,19</sup> These reports indicated that CD4+ count  $< 200$  cells/ $\mu$ L and plasma HIV RNA load  $> 100,000$  copies/ $\mu$ L were predictive of irreparable distal neuropathy not reversible by antiretroviral therapy. This may explain why ART did not result in significant reduction in the severity of neuropathic signs in our patients, even when there was a significant increase in the CD4+ count. The subjective reduction of the mean neuropathic symptoms in

this study may be a reflection of the improvement in the general feeling of well-being and quality of life associated with effective ART.

The fact that there was an overall improvement of DSP in our patients within the 12 weeks of d4T-based ART, suggests that this therapy improved their morbidity. This assertion is corroborated by the results of studies reported by Others.<sup>20–22</sup> However, yet other results have suggested that peripheral neuropathy may be an emerging toxicity associated with the long-term use of d4T.<sup>23,24</sup> These reports are few when compared with those reported with the long-term use of the newer anti-retrovirals, especially the protease inhibitors in the industrial countries.<sup>25</sup> Since d4T has been in use as first-line antiretroviral drug for more than a decade in sub-Saharan Africa, and reports of its neurotoxic effects are still scanty in the literature, it is possible that this long-term effect is under-reported. Thus the need to undertake extensive studies (retrospective and prospective) to investigate this effect on the African population becomes imperative.

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