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Neuropathic Pain in HIV / AIDS Patients on Antiretroviral Therapy and Followed as Outpatients in Bamako, Mali

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Abstract

Introduction: Neuropathic pains induced by HIV/AIDS are frequent and able to negatively impact the life quality of patients and their observance of the treatment.

Objective: We aimed to study the HIV-associated neuropathic pain in infected outdoor patients, followed-up in Bamako (MALI).

Method: We conducted a traversal, prospective, descriptive and analytical study on a cohort of 600 patients. The diagnosis of neuropathic pain was made in patients presenting a sensitive, distal and symmetric neuropathy of legs (DN4 positive). Evaluation was conducted with a simple verbal scale (SVS); the impact on the quality of life was conducted with the following scales: HAD and the short survey on pains; scale of improvement (follow-up).

Results: In this study of 120 patients, 20% had a positive DN4. The age group of [25 to 59] years was the most represented with extremes age of 18 and 75 years and modal age class 36-45 years. Females were predominant. The clinical signs were mainly burns, heaviness, and intense pains. The majority of patients reported moderate to intense pains. These pains had a negative impact on their quality of life (sleep, usual work, walk, humor) as well as treatment observance.

Conclusion: Despite the efforts of international community to make available HAART, without intervention, neurological pains have the possibility to become a real public health problem. In order to reach the pinnacle of universal access to care for HIV/AIDS infected patients, the impact of treatments on patient well-being must be further elucidated.

Keywords: Neuropathic pain; DN4; HIV/AIDS; HAART; Mali; Africa

Introduction

UNAIDS estimates that, in 2011, approximately 34 million people live with HIV/AIDS worldwide and 22.7 million are in Sub-Saharan Africa [1].

The particular susceptibility of the nervous system during the HIV infection is well documented at all stages of the disease: from primo-infection, until AIDS stage [2,3].

As a response to this growing problem, United Nations Members States adopted the global objective of universal access to prevention, treatment, care and support services for 2010 [4]. With this dynamic, UNAIDS, responsible for the riposte against the AIDS pandemic, has defined a global strategy set for 2011-2015 essentially based on aspects of accessibility to care [5].

In Mali, the prevalence of HIV in the general population was 1.6% and 1.3% respectively in 2003 and 2006. In conformity with UNAIDS recommendations, Mali adopted a declaration of national policy against HIV. This declaration sought to ensure free care and drug therapies (HAART as needed) to all HIV patients without prejudice, making Mali the 3rd African country to accept this legislation after Malawi and Senegal [6]. The practice implementation of the universal access to care was materialized, and became widespread to all Health care and counseling units (USAC Its mission was characterized by: prevention, diagnosis, counseling, and follow-up (therapeutic and biologic) for peoples infected or affected by HIV/AIDS [7].

The problem of universal access to care has been studied in other regions of the world similar to Africa. Problems of adherence to HAART remain, despite the efficacy of the molecules this loss of patients due to a lack of adherence to HAART; can reach 20% in some programs [8,9]. These problems adhesion or adherences are less studied in Sub-Saharan Africa. Data from Asia shows the free treatment is not the only condition required to reach the universal access. Other factors such as the offering of service and the quality of life of patients must be taken into account [10].

In those with frequent and disabling pathologies as a result of HIV/AIDS, pain has a negative impact on the quality of life that has been

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well demonstrated [8]. Concerning neuropathic pain, 55% of patients can experience it at all the stages of the disease. This can be directly linked to the virus, to opportunistic infections, or to the toxicity of treatments (HAART or other like TB drugs) [11].

The neuropathic pain induced by HIV or HAART is known for its severity and its resistance to the actually available therapeutics [12,13]. The economic implications of neuropathic pain, despite increased access to care in many developing countries, can increase and become a major public health issue if nothing is done [13,14].

Even though peripheral neuropathies due to Stavudine (d4T) are well documented [7] neuropathic pain during HIV/AIDS is less known in Africa Some studies are available in the literature and were done in western populations with socio-cultural realities, infection determinants, and economic levels vastly different from African reality [15]. Moreover molecules useful for the management of neuropathic pain are not accessible to the majority of African populations, due to the high costs and lack of availability [13,15].

In the present study we focused on pains linked to painful sensitive neuropathies of the legs in HIV positive patients who present within the outdoor health care and counseling unit (USAC) of commune V in Bamako (MALI). Our objective was to study clinical epidemiological characteristics, the consequences of neurologic pains on the quality of life of patients, and the modality of management in the Malian and African context.

Patients and Method

The study design and sample size calculation

We conducted a prospective, descriptive and analytical study at the USAC of commune V in Bamako, Mali. The study focused on HIV infected outdoor patients, with follow-up within the center. The survey took place from 1st March to 31st September 31st, 2009.

The calculated sample size was 120 patients. We used Leslie Kish's formula [16], with a prevalence of 10% (previous data from the register of the center), and a confidence interval of 95%.

Patient enrollment and ethical aspect

600 patients visiting the facility wereconsecutively recruited The inclusion criteria included : adults 18 years and older, appropriate serological status (positive for VIH 1 and/or 2) well documented, followed-up at USAC of commune V, possess sufficient cognitive capacities to understand the questionnaire, and lastly, patients that give informed consent. We randomly enrolled 120 cases presenting with neuropathic pains. The sampling was done according to the arrival order in the center with a step of ¼. The questions were translated to Bambara (the most popular local language) for patients who didn't speak French (the official language) by an expert of the national linguistic department (DENAFLA).

Patients without neurologic pain or those with other causes that can induce neuropathic pain (diabetes, cancer, severe malnutrition, treatments like TB drugs, and other infectious or metabolic diseases, intoxication to alcohol) were excluded.

In Mali, the care of people living with HIV/AIDS is provided by the public sector and civil society: the university hospitals (three in Bamako), regional hospitals and some public structures have monitoring antennae which are generally units with expertise and research functions. Their target consists of inpatient duties; those units called USAC and are affiliated to Medicine ward of health centers of reference (district level) so close to the population within decentralization. USACs are distributed as following: 05 units in Bamako (the capital of Mali) and at least one unit in all administrative regions (08 regions). Our work has focused on a USAC.

We chose the USAC fifth municipality of Bamako for several reasons: (1) Geographically, it is on the outskirts of Bamako, draining populations from urban and semi-urban areas; (2) the experience in the field (it is a pilot center, the first, in Bamako), (3) the importance of attendance (the active cohort count 3525 patients, on average, 60 medical visit are done per day). Our choice was approved by the Scientific Committee against HIV in Mali.

Clinical data

Enrolled patients were examined by the same clinical investigator initially then once a week as a part of an active follow-up, with history followed by neurologic and general examination until 2 months after the initial diagnosis.

At enrollment, the lab test included, in addition to the common HIV test (serology, CD4 count, and viral load), a complete blood cell count, kidney and liver check-up, blood ionogram, syphilis serology (TPHA/VDRL), Viral Hepatitis B Antigen (AgHBs), the blood level of Thyreostimulin hormone, uric acid. The vitamin B12 and folates level were not checked because not available. The patient was enrolled if the pain was distal, symmetric, located at the leg and associated with are flexy. Due to unavailability, an electromyogram was not performed. The diagnoses were made on the basis of DN4 [17]. Patients with a score equal or higher than 4/10 were enrolled as cases of neurologic pain.

For the evaluation of neurologic pain, the simple verbal scale (SVS) was used. The patient was asked to describe his or her own pain according to a scale of 5 categories: No pain; mild pain; moderate pain; intense pain; extremely strong pain [18,19].

For the impact of the pain on the quality of life, the following scales were used:HAD scale (translated in Bambara, national language of the country, for patients that did not speak French), was used to describe the anxiety and depression of the patients [19]. Short questionnaire on pain [20].

A protocol associating two drugs was immediately used with progressive dose: Tricyclic Antidepressor (Amitriptyline), 25 mg/day as initial dose, to increase according to clinical results (by a step of 5 mg each week), to reach a maximal dose of 75 mg per day.

Class II Antalgic (Tramadol), 50 mg per day to increase according to clinical results to reach a maximal dose of 300 mg per day.

For the follow-up of the patients, we used the categorical scale of improvement [18]: increasing of the pain, no improvement, slight improvement, moderate improvement, strong improvement, complete improvement.

Data collection and statistical analysis

Data were collected on an individual case report form containing socio-demographic parameters (age, sex), medical history, clinical signs, lab tests and evolution of patients.

The data entry and statistical analysis were conducted with the SPSS software (version 16.0 Chicago, IL; USA) which was also used for frequency tables and mean calculations. Chi square test was used

for the comparison of proportions with a cut off of significance level of p≤0.05.

Results

Socio demographic data of neuropathic patients

Out of the cohort of 600 HIV-infected patients, 120 had sensitive nerve pain, distal and symmetric according to DN4 (DN4 positive), a frequency of 20%. The majority of patients were aged between 25 and 59 years (91 8%) with extremes of 18 and 75 years and modal age class 36-45 years (33.44%). Females were predominant in this study with a sex ratio of 0.37. The most represented occupational categories were housewives 40% and traders 28.3%. Almost all (92.5%) patients lived in Bamako or in the outskirts of the city (Table 1).

Clinical profile of patients neuropathic

One hundred and three (103) out of the one hundred and twenty (120) patients were taking HAART at the time of inclusion. The molecules used in the majority of patients were nucleoside inhibitors of transciptase inhibitors (NRTIs) and non-nucleoside inhibitors of reverse transcriptase inhibitors (NNRTIs). The first line regimen was prescribed in accordance with national policy, before the gradual replacement of Stavudine (d4T) by Zidovudine (AZT) recommended in 2008, included the combination Stavudine (d4T) + Lamivudine (3TC) in 85.5% patients associated with nevirapine (NVP) in 63% or Efavirenz (EFV) in 22.5% of patients.

Induced pain was generally classified as moderate (47.5%) to severe (38.3%). The neuropathic pain expressed by patients was: burning (50%), paresthesia (72%), numbness (84.2%), tingling (64%), and stabbing pain (80%). Clinical data on the characteristics of the pain and those of the neurological examination are summarized in Table 2.

Table 3 summarizes the impact of pain on quality of life of patients (mood, ability to walk, sleep, normal work, relations with others, love of life.

The impact of pain on quality of life appears more important for patients with neurological pain prior to the initiation of HAART (Table 4).

The presence of anxiety according to the HAD scale was observed in 80% of patients with a score greater than 15, the anxiety was doubtful to 12% of patients with a score lower than 10, and only 8% ofpatients had no anxiety with a score lower than 7. Also according to the scale, depression was seen in 60% of patients with a score greater than 11; depression was doubtful (uncertain), with a score lower than 10% in 20 patients, and 20% of patients had no depressive score.

Variables	Modalities	Numbers	Percents (%)
Age class	18-25 years	8	6.6
	25-59 years	110	91.8
	≥60 years	2	1.6
Sex	Male	33	27.5
	Female	87	72.5
Occupational categories	Housewives	48	40.0
	Traders	34	28.4
	Workmen	19	15.8
	Others *	19	15.8
Residence	Bamako	111	92.5
	Out of Bamako	9	7.5

*others: farmer (6); career (5); student (2); civil servant (2); unemployed (1)

Table 1: Socio-demographic characteristics of patients.

Clinical characteristics of the neuropathy		Yes		Non	
		N	%	N	%
Pain intensity	Low	9	7.5	111	92.5
	Moderate	57	47.5	63	52.5
	Intense	46	38.3	74	61.7
	Very intense	8	6.7	112	93.3
Burning type of pain	Burning type of pain	60	50.0	60	50.0
	Tingling	43	35.8	77	64.2
	Paresthesia	33	27.5	87	72.5
	shooting pain	24	20.0	96	80.0
	Numbness	19	15.8	101	84.2
Deep sensibility disorders		21	17.5	99	82.5
Motor disorders		40	33.3	80	66.7
Achilles tendon reflex abolished		120	100	00	00

Table 2: Distribution of patients according to the clinical characteristics of neuropathy.

All 120 patients had been able to make a causal link between HIV/AIDS and pain, and 28 (23%) patients had considered stopping treatment.

After two months of treatment (Amitriptilline and Tramadol), we observed the following situation: Complete relief (16 patients, 13.33%), high relief (17 patients, 14, 16%), moderate relief (57 patients, 47 5%), low relief (15 patients, 12, 5%), no change (12 patients, 10%), worsening (3 patients, 2.5%)

ARV treatment was continued without interruption or changing of regimens. Adverse events did not require treatment analgesic discontinuation and we observed these events during the study: somnolence more or less annoying at the beginning of treatment (65%), dry mouth (58%), digestive disorder type nausea or vomiting (48%), dizziness (25%).

Discussion

This study aimed to determine the prevalence, intensity, associated factors, and impact of pain in outpatients of the Care and Counseling Unit in the fifth municipality of Bamako in Mali.

In a cohort of 600 patients examined in our study, 20% had neurological pain according to DN4. This incidence is on average significantly lower than that observed by 30% to 47% of authors [14,15], but higher than others [21,22]. This discrepancy is probably due to the inclusion criteria and patient profile (inpatient vs. outpatient and diagnostic tool).

In Nigeria, a country with demographic similarities to Mali, a study of 323 patients showed a prevalence of painful neuropathy of 39% [23]. In a South African study, with 598 patients, the prevalence of neuropathic pain was 30% [24].

The particularity of these two studies is the recruitment criteria of neuropathic pain. In the first study, it was at least one sign, and in the second study, two signs in relation to neuropathic pain. Our study differs from the previously mentioned ones, due to the use of the DN4 scale. Using this method, the diagnosis of neuropathic pain is improved; the scale is extensively validated with 83% sensitivity and 90% specificity in the diagnosis of neuropathic pain [17,19].

Accessibility to HAARTs is a reality in Mali. However, despite this remarkable progression in the fight against HIV/AIDS, painful peripheral neuropathy, due in large majority to Stavudine (d4T)

Impact of pain on	Mood n (%)	Ability to walk n (%)	Normal Work n (%)	Sleep n (%)	Relation with others n (%)	Love of life n (%)
Do not bother	63 (52.5)	21 (17.5)	47 (39.2)	22 (18.3)	91 (75.8)	85 (70.8)
Enough discomfort	54(45.0)	71 (59.2)	66 (55.0)	65 (54.2)	27 (22.5)	34 (28.3)
Discomfort completely	3 (2.5)	28 (23.3)	7 (5.8)	33 (27.5)	22 (1.7)	1 (0.8)

Table 3: Impact of peripheral neuropathy on the life quality of patients.

Impact on \ Setting of neuropathic pain		Before ART N (%)	<1 month on ART N (%)	≥1 month on ART N (%)	Total N (%)	p
Mood	Yes	15 (88.2)	27 (42.2)	15 (38.5)	57 (47.5)	**10^{-3}**
	No	2 (11.8)	37 (57.8)	24 (61.5)	63 (52.5)	
Ability to walk	Yes	16 (94.1)	49 (76.6)	34 (87.2)	99 (82.5)	0.15
	No	1 (5.9)	1 5 (23.4)	5 (12.8)	21 (17.5)	
Normal work	Yes	15 (88.2)	38 (59.4)	20 (51.3)	73 (60.8)	**0.03**
	No	2 (11.8)	26 (40.6)	19 (48.7)	47 (39.2)	
Sleep	Yes	17 (100)	49 (76.6)	32 (82.1)	98 (81.7)	0.08
	No	0 (0)	15 (23.4)	7 (17.9)	22 (18.3)	
Relations with others	Yes	4 (23.5)	14 (21.9)	11 (28.2)	39 (32.5)	0.76
	No	13 (76.5)	50 (78.1)	28 (71.8)	91 (67.5)	
Love of life	Yes	11 (64,7)	14 (21,9)	10 (25,6)	35 (29,2)	**0.002**
	No	6 (35,3)	50 (78,1)	29 (74,4)	85 (70,8)	
Total		17 (100)	64 (100)	39 (100)	120 (100)	

Table 4: Impact of peripheral neuropathy on the life quality of patients according to de period of setting.

Country	Drugs (Price in euro)					Minimum wage
	Neurontin® Gabapentine	Lyrica 75mg® Prégabaline	Topalgic 100® Tramadol	Laroxyl 25 mg® Amitriptilline	Tegretol® Carbamazepine	
Mali			68.70			
Benin		83.05	19.85	5.46		31.98
Cameroon			4.19	5.31	9.45	53.44
Ivory Coast	68.5	53.44		5.34	12.98	38.17
Djibouti	61	38	5	7.5	9.14	55.95
Morocco	67.34	116.6	21.7	16.47	8.95	
Niger	53.43	49	Not Avail.	3.87	9.59	200
Senegal	87.36	65.65	16.64	5.5	8.7	42.74
Togo	53.78	48.12	4.26	6.30	10.2	72.82

Table 5: Availability and affordability of medicines in various African countries.

remains a major problem. These neuropathies have been shown to have a significant impact on the well-being of patients [25,26].

The presence of Stavudine in all treatment protocols of patients could largely explain the occurrence of this pain. The inducing effect of peripheral neuropathy nucleoside inhibitors of reverse transcriptase (Stavudine) is well known in the literature, especially in Africa [23,24]. It was withdrawn officially in Mali in 2010.

The predominance of housewives and men traders should be noted. The feminization of the HIV infection in Africa is well known (ref). , We have already reported this feature in a study of the spread of HIV in Mali [27]. In particular, the infection of Women in Africa lies on their financial dependence on men [27]. Regarding male traders, it is often a group of people moving for professional reasons, and Africa has shown that these men acquire new high-risk behaviors as they change their environment [28].

Painful neuropathy related to HIV/AIDS is on the rise despite the increasing availability of ARVs in many countries. The risk factors identified and associated with the onset of the pain are the neurotoxicity of Stavudine, senescence, lower CD4+ T cells, in addition to comorbidity factors such as diabetes mellitus, malnutrition, and exposure to isoniazid [26].

Recent genetic studies have identified genes that affect mitochondrial function, and genes involved in the inflammatory response that increase the risk of occurrence of painful neuropathy in patients exposed to ARVs [25,29].

Regarding clinical neurological pain, the majority of our patients reported moderate to severe pain, consistent with the literature data [15]. In an American study focused on 1539 patients, the majority of patients reported paresthesia generally moderate, and only (13) 4% of patients noted mild pain and (number) 7.9% severe pain [26].

Regarding the impact of pain on the well-being of patients, we showed that the trouble was particularly significant in walking ability, mood, normal work and sleep. The evaluation on the HAD scale noted that the majority of our patients presented an anxiety-depressive state and this concurred with many other studies [15,23,25,26]. In the multicenter Namisango in East Africa, the authors were able to establish a link between the intensity of the pain and degradation of the quality of life of patients [15].

On the therapeutic hand, neurological pain in HIV/AIDS is known for its resistance to standard treatment, despite a better understanding of underlying pathophysiological mechanisms [14]. Faced with this perplexing problem and lacking clear guidelines, a panel of expert South Africa (the country most affected by HIV in Africa) proposed recommendations [16].

In the context of developing countries, HIV management has two major, especially in Africa: (1) the available therapeutic arsenal has low efficiency; (2) the availability and accessibility of molecules are insufficient. Table 5 shows the situation of the availability and accessibility of the molecules with respect to the minimum wage in some African countries.

Conclusion

Studies such as the current one confirm the high frequency of neurologic pain during HIV/AIDS. Despite the efforts of the international community to make HAART accessible, neurological pains will become a real public health problem if no action is taken.

With these results and those of previous studies, it is presently clear that free antiretroviral treatment is not the singular condition necessary to reach the ideals of universal access. Other factors include such as the availability of service, must be understood.

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